SEPTEMBER 28, 1957 Per (sec. 8) PAGES 605 TO 652

THE LANCET

Offices: 7, ADAM STREET, ADELPHI, W.C.2
Telegrams: LANCET, RAND, LONDON Telephone: TEMPLE BAR 7228 and 7229

No. XIII OF VOL. II, 1957 LONDON, SATURDAY, SEPTEMBER 28, 1957 Pp. 96—Price 1s. 6d.
No. 6996 VOL. CCLXXIII Founded 1823 PUBLISHED WEEKLY Registered as a Newspaper Annual Subscription: £3 3s.

6 OCT 17 1957
Cont. Copy

A quick-acting short-term analgesic

'PROPONESIN'
TRADE MARK

TABLETS each containing 100 mg. of tolpronine hydrochloride.

For relief of pain in herpes zoster, dysmenorrhoea, toothache, headache, sinusitis, backache.

DOSAGE: One or two tablets three or four times a day. Bottles of 10 at 1/8; 50 at 5/-; 250 at 17/6. *Purchase tax extra.*

THE BRITISH DRUG HOUSES LTD. (Medical Department) LONDON N.1

THE ESSENTIALS OF FORENSIC MEDICINE
By CYRIL JOHN POLSON, M.D., F.R.C.P.
Barrister-at-Law; Professor of Forensic Medicine University of Leeds

"It is superbly done, for he writes well, lucidly, and sanely, weaving the vivid and the more mundane chapters of forensic medicine, medical ethics, law and insanity into a comprehensive whole that is both informative and readable."—*The Lancet.*

562 pages 30s. net, plus 1s. 6d. postage
The English Universities Press Ltd., 102, Newgate-street, London, E.C.1

Sixth Edition *Now available*

PRINCIPLES OF MEDICAL STATISTICS
By A. BRADFORD HILL, C.B.E., D.Sc., Ph.D., F.R.S.
Demy 8vo 314 + x 10s. 6d. net, plus 10d. postage
Revised and enlarged (containing a new chapter on Clinical Trials and 16 pages of random sampling numbers).
The Lancet Limited, 7, Adam-street, Adelphi, London, W.C.2.

UNITED STATES OF AMERICA AND CANADIAN SELLING RIGHTS HELD BY OXFORD UNIVERSITY PRESS, INC.
114, Fifth Avenue, New York, 11, N.Y., U.S.A.

Third Edition

INTRODUCTION TO DISEASES OF THE CHEST
By JAMES MAXWELL, M.D. (Lond.), F.R.C.P. (Lond.)
Physician, Royal Chest Hospital; Physician to the Ministry's Mass X-ray Unit; Consulting Physician, Royal National Sanatorium, Bournemouth; late Physician, St. Bartholomew's Hospital.
Demy 8vo 308 + xii 66 Half-tone Illustrations
12s. 6d. net, plus 1s. 4d. postage.
Hodder & Stoughton, Ltd., 20, Warwick-square, London, E.C.4

HOW TO USE A MEDICAL LIBRARY
By L. T. MORTON, A.L.A.
Information Officer, British Medical Association.
44 pages 5s. net
Wm. Heinemann Medical Books Ltd., 99, Gt. Russell St., W.C.1

HOW TO WORK—
ADVICE TO STUDENTS STARTING MEDICINE.
An address to the London Hospital Medical Society.
By A. E. CLARK-KENNEDY, M.D. Camb., F.R.C.P.
Demy 8vo. 16 pages. Price 1s.
The Lancet Limited, 7, Adam-street, Adelphi, London, W.C.2

CAREERS IN MEDICINE
Edited by P. O. WILLIAMS, M.A. (Cantab.), M.B., B.Chir., M.R.C.P.
With contributions from 49 eminent medical authorities
Cr. 8vo 292 pages Price 15s. net, plus 1s. 4d. postage
This book outlines the particular qualities of mind, the type and amount of specialised training, required in each branch of the Medical Profession.
"... it should be in the hands of everyone who has to advise medical students, and certainly should be consulted by every newly-qualified doctor."—*The Practitioner.*
Hodder & Stoughton Ltd., 20, Warwick-square, London, E.C.4

IN THE MENTAL HOSPITAL
Eleven articles reprinted from THE LANCET.
A group of articles chiefly concerned with the value of active occupation and work for mental patients and the means whereby it is best provided.
72 pages. Price 2s. 6d. (postage 4d.)
The Lancet Limited, 7, Adam-street, Adelphi, London, W.C.2

JUST PUBLISHED

THE DIAGNOSIS AND TREATMENT OF INFECTIONS
D. GERAINT JAMES
The aim of this book is to synthesise the clinical and laboratory aspects of infectious diseases for the student and practitioner. Dr. James' lucid text and informative tables combine to make his book a practical and readily intelligible guide to a subject the study of which becomes ever more complex with the increasing use and variety of chemotherapeutic agents.
244 pages 24 tables 30s.

AN INTRODUCTION TO FUNCTIONAL ANATOMY
DAVID SINCLAIR
Professor Sinclair provides a simple account of human anatomy and physiology written round the syllabus of the Association of Occupational Therapists, but suitable also for physiotherapists and members of the other ancillary medical sciences. His book will be particularly valuable to students previously obliged to glean their knowledge of anatomy from the larger medical textbooks.
428 pages 168 illustrations 42s.

BLACKWELL SCIENTIFIC PUBLICATIONS · OXFORD

A search for the causative origin of asthma can indeed be a tedious one, but always the underlying factor—BRONCHOSPASM—can be treated immediately with FELSOL. Physicians in all parts of the world to which it has been introduced, have for years relied implicitly on FELSOL for the instant relief it gives in an attack of asthma, no matter what the basic cause. FELSOL acts directly on the bronchial musculature and indirectly through the vagus and sympathetic.

Rapid in action — Prolonged in effect

Full relief in perfect safety

Clinical sample and literature on request

BRITISH FELSOL COMPANY LTD., 206/212, ST. JOHN STREET, LONDON, E.C.1

BROADER SPECTRUM
for Greater Protection

Combining the orally effective Penicillin-V with three sulphonamides, this pleasant fruit-flavoured suspension is ideal for the treatment of bronchitis, otitis media, urinary and other mixed infections in young children. The joint attack provided by Penicillin-V and the sulphonamides is particularly valuable where the causative organism is only moderately susceptible to penicillin alone.

Each 5 cc. contains:	62.5 mg. Penicillin-V-Lilly 0.25 Gm. Sulphonamides
Average dose:	½ to 2 teaspoonfuls every six hours
Packing:	Bottles to make 60 cc.
	Also available:
	Tablets Penicillin-V-Sulpha Lilly

SUSPENSION

PENICILLIN-V-SULPHA LILLY
PAEDIATRIC

Lilly

ELI LILLY & COMPANY LIMITED, BASINGSTOKE, ENGLAND

SEPT. 28, 1957 PAGES 605 TO 652

THE LANCET

A JOURNAL OF BRITISH AND FOREIGN MEDICINE, SURGERY, OBSTETRICS, PHYSIOLOGY, PATHOLOGY, PHARMACOLOGY, PUBLIC HEALTH, AND NEWS

No. 6996 LONDON: SATURDAY, SEPTEMBER 28, 1957 CCLXXIII

CONTENTS

THE WHOLE OF THE LITERARY MATTER IN THE LANCET IS COPYRIGHT

ORIGINAL ARTICLES

Mecamylamine — ARTHUR KITCHIN, M.B.C.P., CLIFTON LOWTHER, F.R.F.P.S., RICHARD TURNER, F.R.C.P. ... 605

A Trial of Two Antituberculous Drugs — G. W. ALLAN, M.R.C.P.E., W. MCNAUGHT, M.B., A. W. LEES, F.R.C.P.E. ... 609

Sensitivity of *Mycobacterium tuberculosis* to Para-aminosalicylic Acid, Isoniazid, and the P.A.S. Salt of Isoniazid — J. M. DUNBAR, M.D., R. T. RITCHIE, M.B.C.P.E. ... 612

Carcinoma of the Œsophagus — J. LEIGH COLLIS, F.R.C.S. ... 613

Deficiency of Antihæmophilic Globulin in Heterozygous Hæmophilic Females — A. S. DOUGLAS, M.R.C.P., I. A. COOK, M.B. ... 616

The Incidence of Pathogenic *Escherichia coli* in Routine Fæcal Specimens — D. R. GAMBLE, M.B., K. E. K. ROWSON, M.B. ... 619

Plasma-insulin Estimation by the Rat-diaphragm Method — P. H. WRIGHT, M.B. ... 621

PRELIMINARY COMMUNICATIONS

Effect of Corticotrophin on Urinary Excretion of Pregnanediol and Pregnanetriol — J. D. N. NABARRO, F.R.C.P., A. MOXHAM ... 624

The Acidity of the Urine and the Excretion of Ammonium in Renal Disease — H. E. F. DAVIES, M.R.C.P., OLIVER WRONG, M.R.C.P. ... 625

NEW INVENTIONS

Vein-holding Forceps — HAROLD DODD, F.R.C.S. ... 625

SPECIAL ARTICLES

Gravity Air-displacement Pressure Steam Sterilisers — A. C. SCOTT, M.B. ... 633

Medical Defence Union ... 637

REVIEWS

Notices of Books ... 626

LEADING ARTICLES

Cars and Drivers ... 627

Symposium on Nuclear Sexing 628

ANNOTATIONS

Trials of New Antituberculous Agents ... 629

Citric Acid and Urolithiasis ... 630

Left-heart Catheterisation ... 630

Discography ... 631

Weight Changes after Gastrectomy ... 632

SYMPOSIA

Nuclear Sex ... 637

LETTERS TO THE EDITOR

Influenza (Prof. J. W. McLeod, M.B., F.R.S.) ... 639

"Pneumoconiotic Neurosis" (Dr. Norman Macdonald) ... 639

Treatment of Migraine (Dr. Gordon Ambrose) ... 639

Inadequacy of General Anæsthesia for Abdominal Operations (Dr. D. A. B. Hopkin) ... 640

Nervous System in Porphyria (Dr. J. B. Gibson) ... 640

Instrument for Taking Specimens for Cervical Culture (Dr. Bernard Sandler) ... 640

Consultant and Specialist (Mr. T. Yeadon) ... 641

The Wolfenden Report (Dr. R. C. Webster) ... 641

Apartheid in Nursing (Miss G. Khala) ... 641

A New Disease? (Dr. H. M. Sinclair) ... 642

High-pressure Oxygen and Radiotherapy (Dr. G. E. Loxton) ... 642

Classification of Gastric Ulcers (Dr. J.-Jacques Spira) ... 642

A Vibrating Bed for Ankylosing Spondylitics (Dr. F. Dudley Hart, Mr. H. J. Ridgeway, M.I.H.E.) ... 642

Fainting and Cerebral Damage (Dr. F. F. Cartwright) ... 643

Polythene and Polyvinyl Tubing for Bladder Catheters (Prof. J. Chassar Moir, F.R.C.O.G.) ... 643

Cardiac Catheterisation (Dr. G. R. Graham) ... 643

Prevention of Maternal Deaths (Mr. R. F. Lawrence, M.R.C.O.G.) 644

Deficiency of an Extra-thyroid Enzyme in Sporadic Cretinism (Dr. J. H. Hutchison, Dr. G. C. Arneil, Dr. E. M. McGirr) ... 644

Cystoscopy in the Investigation of Post-menopausal Bleeding (Mr. W. G. Mills, F.R.C.S.) ... 644

Insulin in Early Schizophrenia (Dr. William Sargant) ... 644

Cardiac Arrest during Halothane Anæsthesia (Dr. A. R. Hunter) 645

Medical Students Look West (Sir John Conybeare, F.R.C.P.; Mr. R. D. Cohen, B.A., Mr. D. T. Hughes, B.SC., Mr. Peter Richardson, B.SC.) ... 645

Placebos and Placebos (Mr. Conrad Chyatte, PH.D.) ... 646

Cork-retainer for Transfusion Set (Dr. R. N. G. Atherstone) ... 646

Gastrojejunal Intussusception Due to Benign Gastric Leiomyoma (Miss Betty Underhill, F.R.C.S.) 646

Acne Vulgaris (Dr. E. L. Cohen) 647

Infusion Needles (Dr. J. H. Waelsch) ... 647

Management of Anastomotic Ulcer (Mr. Harold Burge, F.R.C.S.) ... 647

Polythene Giving-sets for Transfusion (Dr. R. R. Thomas) ... 647

Bone-marrow for Treatment of Leukæmia (Dr. D. W. van Bekkum, Prof. J. A. Cohen, M.D.) ... 647

PUBLIC HEALTH

Influenza ... 648

Poliomyelitis ... 648

Eradication of Tuberculosis in Cattle ... 648

OBITUARY

Hugh MacLean ... 649

David Turnbull Richardson ... 649

James Mackinnon ... 650

Vera Norris ... 651

NOTES AND NEWS

Overtime in Mental Hospitals ... 651

Money for Discovery ... 651

Diary of the Week ... 648

Appointments ... 651

Births, Marriages, and Deaths ... 651

New Books

AORTOGRAPHY
Its Application in Urological and some other Conditions
By W. BARR STIRLING, Ch.M., F.R.C.S.Ed., F.R.F.P.S.G.
300 pages. 160 illustrations. 50s.

THE FOREQUARTER AMPUTATION
By H. F. MOSELEY, M.A., D.M., M.Ch., F.R.C.S. (England and Canada), F.A.C.S.
88 pages. 100 illustrations 42s.

THE STUDENT LIFE
The Philosophy of Sir William Osler
Edited by RICHARD E. VERNEY, M.B., Ch.B., D.R., F.R.C.P.E.
228 pages. 15s.

New Editions

THE CLOSED TREATMENT OF COMMON FRACTURES
Second Edition. By JOHN CHARNLEY, M.B., B.Sc., F.R.C.S.
270 pages. 385 illustrations. 50s.

MEDICAL JURISPRUDENCE AND TOXICOLOGY
Tenth Edition. By JOHN GLAISTER, J.P., D.Sc., M.D., F.R.S.E. In collaboration with EDGAR RENTOUL, M.B.E., M.A., LL.B., M.B., Ch.B.
732 pages. 287 illustrations. 47s. 6d.

COMBINED TEXTBOOK OF OBSTETRICS AND GYNÆCOLOGY
Sixth Edition. Edited by DUGALD BAIRD, B.Sc., M.D., D.P.H., F.R.C.O.G.
948 pages. 633 illustrations. 95s.

E. & S. LIVINGSTONE LTD., TEVIOT PLACE, EDINBURGH

THE SEARCH FOR VITAMINS

Unlike most natural substances, vitamins were appreciated long before they were identified and their chemical and physiological properties were studied. Thus, beriberi in the Japanese navy was controlled by dietary measures several decades before the isolation of thiamine.

Marmite, too, was popular long before its vitamin content was suspected and before its beneficial effects in nutritional macrocytic anaemias and in vitamin B complex deficiencies were recognised. Its haemopoietic properties were demonstrated in 1931 and subsequent analysis showed the presence of folic acid, as well as riboflavin, nicotinic acid, choline, pyridoxine, pantothenic acid, inositol, biotin, vitamin B_{12} and p-aminobenzoic acid. Marmite is palatable and easily administered. It therefore constitutes a useful source of these vitamin B factors.

MARMITE
yeast extract

Literature on request

MARMITE LIMITED, 35 SEETHING LANE, LONDON E.C.3
(5601)

YOUR CHILD

In your plans for your child's education and career life assurance can be a real help. Write today for a copy of the New "Career Policy" leaflet to

SCOTTISH WIDOWS' FUND

Head Office: 9 St. Andrew Square, Edinburgh, 2
London Offices: 28 Cornhill, E.C.3 17 Waterloo Place, S.W.1

Elastoweb **heavy cotton elastic bandage**

now prescribable on E.C.10

Elastoweb is a non-adhesive heavy cotton elastic bandage used for the compression treatment of leg conditions, particularly those requiring extra firm support.

Elastoweb has for many years been supplied only to hospitals. Now it is included in the Drug Tariff.

Elastoweb is 3" wide x 2 yds. (unstretched). Stretched length 6/7 yds. It is flesh coloured and fitted with a special footloop.

an S&N product SMITH & NEPHEW LTD., WELWYN GARDEN CITY, HERTS.

BOOKS for AUTUMN USE

A New Ciba Foundation Volume — *Just Published*

COLLOQUIA ON ENDOCRINOLOGY

Vol. 11.—**Hormones in Blood**

74 Illustrations. 56s.

PROGRESS IN CLINICAL MEDICINE
Edited by RAYMOND DALEY, M.A., M.D., F.R.C.P., and HENRY MILLER, M.D., F.R.C.P., D.P.M.
Third Edition. 36 Illustrations. 40s.

THE PRACTICE OF MEDICINE
Edited by J. S. RICHARDSON, *M.V.O.*, M.A., M.D., F.R.C.P.
86 Illustrations. 40s.

PRACTICAL PROCEDURES IN CLINICAL MEDICINE
Biochemical and Radiological Investigations
By R. I. S. BAYLISS, M.A., M.D., F.R.C.P.
Second Edition. 61 Illustrations. 32s.

THE CLINICAL APPROACH IN MEDICAL PRACTICE
By G. E. BEAUMONT, M.A., D.M., F.R.C.P.
74 Illustrations. 45s.

CHILD HEALTH AND DEVELOPMENT
By various authors. Edited by R. W. B. ELLIS, *O.B.E.*, M.A., M.D., F.R.C.P.
Second Edition. 81 Illustrations. 42s.

ESSENTIALS OF ORTHOPÆDICS
By PHILIP WILES, M.S., F.R.C.S., F.A.C.S.
Second Edition. 7 Coloured Plates and 393 Text-figures. 55s.

PROGRESS IN CLINICAL OBSTETRICS AND GYNÆCOLOGY
By T. L. T. LEWIS, M.B., F.R.C.S., M.R.C.O.G.
90 Illustrations. 55s.

PRINCIPLES OF EPIDEMIOLOGY
By IAN TAYLOR, M.D., M.R.C.P., D.P.H., and JOHN KNOWELDEN, M.D., D.P.H.
25 Illustrations. 30s.

GERMAN-ENGLISH MEDICAL DICTIONARY
Containing words currently used in medical, pharmaceutical and allied professions
Compiled by W. O. GOULDEN, B.A., Dr.Phil.
520 Pages. 45s.

HIGH BLOOD PRESSURE
By Sir GEORGE PICKERING, M.A., M.B., M.D. Ghent, F.R.C.P.
106 Illustrations (5 in Colour). 65s.

THE DIABETIC LIFE
Its Control by Diet and Insulin
A Concise Practical Manual for Practitioners and Patients
By R. D. LAWRENCE, M.A., M.D., F.R.C.P.
Fifteenth Edition. 19 Illustrations. 12s. 6d.

PRACTICAL HÆMATOLOGY
By J. V. DACIE, M.D., M.R.C.P.
Second Edition. 43 Illustrations. 20s.

J. & A. CHURCHILL Ltd., 104 GLOUCESTER PLACE, LONDON, W.1

Just published by
The Year Book Publishers Inc., Chicago:

A new volume in the series
Annual Year Books:

YEAR BOOK OF CANCER
1956-57

Edited by R. L. CLARK, Jr.
and R. W. CUMLEY
Houston, Texas

The purpose of the Year Book of Cancer is to provide comprehensive abstracts of significant articles in the field of oncology, which have appeared during the preceding year.

1957 5 × 7 572 pages 57s

Distributed in the United Kingdom by
INTERSCIENCE PUBLISHERS, LTD.
88-90 Chancery Lane, London, W.C.2

RECENT PUBLICATIONS

SPORTS INJURIES
Their Prevention and Treatment
By DONALD F. FEATHERSTONE
204 *pp., with* 48 *illustrations* 35s., *post* 1s. 2d.
A book for physiotherapists and all others connected with the hazards of sport.

A SYNOPSIS OF OTORHINOLARYNGOLOGY
By J. F. SIMPSON, I. G. ROBIN, and J. C. BALLANTYNE
458 *pp., with* 88 *illustrations* 42s., *post* 1s.
Supplements the larger text-books and forms an ideal aid to revision.

STRUCTURAL PSYCHOLOGY
De Humani Mentis Fabrica
By D. and K. STANLEY-JONES
188 *pp.* 21s., *post* 11d.
Written primarily for doctors, the main theme of the book is the unity of mind and brain.

THE QUICKSILVER DOCTOR
The Life and Times of Thomas Dover
By KENNETH DEWHURST
192 *pp., with* 12 *plates* 21s., *post* 1s.
A fascinating book for bedside reading.

MEDICAL ANNUAL, 1957
Edited by SIR HENRY TIDY and R. MILNES WALKER
570 *pp. Fully illustrated* 38s. 6d., *post* 1s. 9d.
The seventy-fifth issue of this indispensable work of reference.

JOHN WRIGHT & SONS LTD., BRISTOL

In Dysmenorrhoea and Menopausal Disorders

combining Dienoestrol and Phenobarbitone

ARMO-NOESTROL

TABLETS

Each tablet contains
Dienoestrol 0.1 mg.
Phenobarbitone 16 mg.

A

FORTE

Each Forte tablet contains
Dienoestrol 0.3 mg.
Phenobarbitone 16 mg.

Available in bottles of 100 and 500.

Write for literature to :

THE ARMOUR LABORATORIES
(Armour and Company Limited)
Hampden Park, Eastbourne, England
Telephone : Hampden Park 740. **Telegrams : Armolab, Eastbourne**

FRIEND OF THE FAMILY

WISE ADVICE about reliable methods of planned parenthood allays anxiety and inspires the mutual trust and intimate assurance necessary for lasting health and happiness in marriage.
Gynomin and Antemin are alternative types of contraceptives. Their efficient action satisfies modern requirements and both may be recommended by the medical profession.

GYNOMIN

The ideal antiseptic and deodorant contraceptive in tablet form. Simple and pleasant in use, scientifically functional in formula, and spermicidally efficient in result.
Formula : Sodium Bicarbonate B.P. 12.7, Tartaric Acid 11.1 Chloramine B.P. 1.1, Perfume q.s., Excipients to 100.

ANTEMIN

A cosmetic-like antiseptic cream, with high spermicidal efficiency. Non-irritant and non-toxic. Simply applied and odourless. May be used with or without an occlusive cap.
Formula : Sodium dioctyl sulphosuccinate 0.25, Ricinoleic Acid B.P. 1.00, Boric Acid B.P. 1.00, Paraformaldehyde B.P.C. 0.15, Base to 100.

The Family Planning Association advise that, for maximum safety, any chemical contraceptive should be used with a mechanical barrier.

Medical literature and samples on request

COATES & COOPER LTD.

PYRAMID WORKS · WEST DRAYTON · MIDDLESEX

How severe a gastric irritant is aspirin?

FURTHER RESEARCH has now been done into the irritant effects of aspirin upon the gastric mucosa. A detailed report on this work appears under the heading "Aspirin and Ulcer" in the B.M.J., July 2nd, 1955.

The summary of the discussion appended to this report is as follows:

"Aspirin is a serious gastric irritant, particularly in peptic ulcer patients."

Here is a further extract from the report:—"In conclusion it is suggested that aspirin should never be given to patients with peptic ulceration, or indeed to those who have any gastric intolerance to it, however mild. Such an instruction should be given a prominent place in peptic ulcer advice charts, usually in place of much that could be safely left out. Some of these patients took aspirin on a full stomach only in powder form, with serious results, and, although this method almost certainly mitigates its irritant effects, it does not guarantee immunity. Calcium aspirin does not have this irritant action unless it has deteriorated through standing, and it can be used with impunity, especially if prescribed in soluble form. This simple measure would, in our opinion, cut down significantly, the incidence of haematemesis and exacerbations of ulcer symptoms."

SOLPRIN provides calcium aspirin in pure and stable form.

CODIS is a compound tablet that provides codeine and phenacetin and calcium aspirin, in place of the ordinary aspirin in Tab. Codein. Co. B.P.

Neither SOLPRIN nor CODIS is advertised to the public.

RECKITT AND COLMAN LTD., HULL & LONDON (PHARMACEUTICAL DEPT. HULL)

Napkin Rash

PREVENTION and treatment

DRAPOLENE is a cream formulated specifically for the prophylaxis and treatment of urinary dermatitis.

DRAPOLENE CREAM

PRESCRIBE DRAPOLENE BY NAME

The water miscible property of the cream allows ease of application and facilitates the napkin toilet. The application of DRAPOLENE to both mild and severe forms of urine rash provides a soothing effect which gives relief from the distress associated with all forms of urine rash. Many infant welfare centres confirm that even the severest cases respond satisfactorily in four to six days.

FORMULA

Benzalkonium chloride, 0.01% in a water miscible base.

PACK

2oz. tubes.
1lb. dispensing jars.

CALMIC LIMITED, CREWE. *Phone CREWE 3251-5* **LONDON:** *2 Mansfield St., W.1. Phone LANgham 8038-9*

AUSTRALIA: 458-468 Wattle Street, Ultimo, Sydney, N.S.W

CANADA: Terminal Building, York St., Toronto.

DI

Butazolidin

REGD. TRADE MARK

In Superficial thrombophlebitis

Butazolidin's outstanding reputation in the treatment of rheumatic disorders should not overshadow its value in rapidly relieving pain and swelling and in restoring normal temperature in superficial thrombophlebitis.

It is rarely necessary for treatment to last more than one week.

Geigy

Detailed literature is available on request.

Geigy Pharmaceutical Company Ltd.,
Wythenshawe, Manchester, 23

PH.103

Ortho

new

most spermicidal contraceptive
from Ortho research

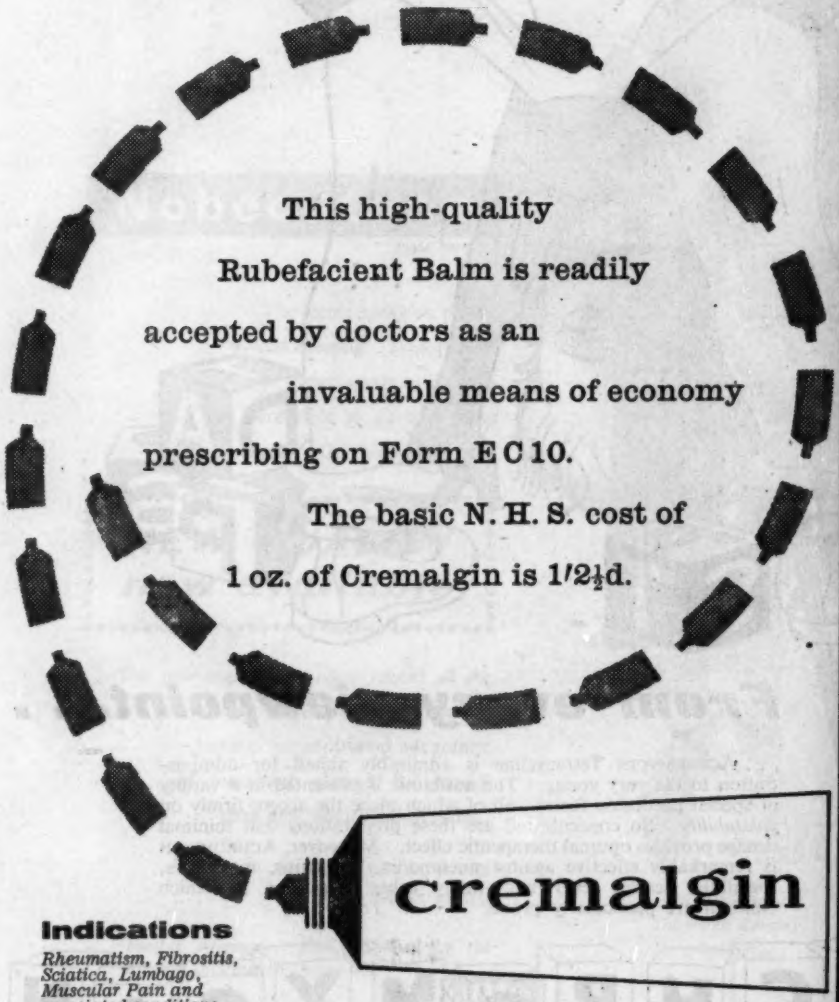
The unmatched potency of Delfen vaginal cream is due to its new chemical spermicidal agent which invades every vaginal crevice by the rapid release action of a new emulsified oil-in-water base

Delfen vaginal cream:
nonylphenoxypolyethoxyethanol 5.00%
in an oil-in-water emulsion at pH 4.5
LITERATURE ON REQUEST

Ortho Pharmaceutical Limited · High Wycombe · England

Reduce the average cost — prescribe Cremalgin

ECONOMY PRESCRIBING



This high-quality Rubefacient Balm is readily accepted by doctors as an invaluable means of economy prescribing on Form E C 10.

The basic N. H. S. cost of 1 oz. of Cremalgin is 1/2½d.

cremalgin

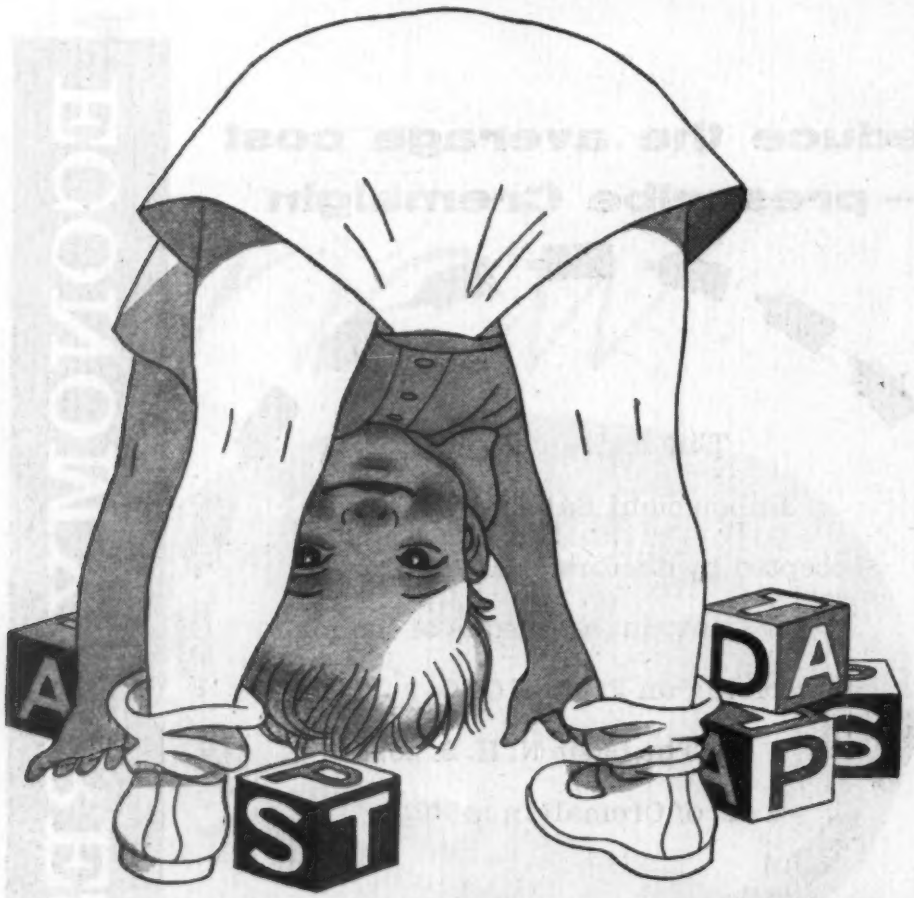
Indications

Rheumatism, Fibrositis, Sciatica, Lumbago, Muscular Pain and associated conditions.

Methyl Nicotinate 1.0%
Glycol Salicylate 10.0%
Histamine Dihydrochloride 0.1%
Capsicin 0.1%
Excipient q.s.

WEST PHARMACEUTICAL COMPANY LIMITED

82 Victoria Street, London, S.W.1. Telephone: TAT 2580



From every viewpoint. . .

. . . ACHROMYCIN Tetracycline is admirably suited for administration to the very young. The antibiotic is presented in a variety of special paediatric forms—all of which place the accent firmly on *palatability*. So concentrated are these preparations that minimal dosage provides optimal therapeutic effect. Moreover, ACHROMYCIN is remarkably effective against pneumonia, bronchitis, meningitis, tonsillitis, scarlet fever and many other infections to which children are particularly prone.

ACHROMYCIN* TETRACYCLINE

PAEDIATRIC PRESENTATIONS

SYRUP (125 mg. per cc.): Bottles of 2 and 16 fl. oz. · SOLUBLE TABLETS (50 mg.): Bottles of 100 · LIQUID PAEDIATRIC DROPS 1 Gram in 10 cc. bottle · FOR ORAL SUSPENSION 1.5 Gram in 1 oz. bottle: SPERSOIDS ° Dispersible Powder (50 mg. per 5 Gm.) Jars of 38 Gm. and 75 Gm.

*REGD. TRADE MARK

LEDERLE LABORATORIES DIVISION

Cyanamid OF GREAT BRITAIN LTD., London, W.C.2

Designed for Protection...

Nobecutane
Trade Mark

The sterile spray-on plastic wound dressing. Transparent, impermeable to bacteria but permeable to air and water vapour. Washable but waterproof.

NEW QUALITY now available

The new improved quality retains all the advantages of the original product, but has the **additional advantage of remaining cleaner for longer than any traditional dressing.**

Available in 50 ml. bottles and 100 & 300 ml. sprays.

Further information gladly supplied by the Medical Information Department

An example of Thirteenth Century Armour

EVANS MEDICAL

EVANS MEDICAL SUPPLIES LIMITED
SPEKE, LIVERPOOL 19 · (HUNTS CROSS 1881)
London Office: Ruislip, Middlesex (Ruislip 3333)

1004

The esters of NICOTINIC, SALICYLIC and p-AMINOBENZOIC acids bring relief to cases of arthritis and rheumatism

"Thank you, doctor"

IN CASES OF soft-tissue rheumatism, and arthritic disorders, many doctors are tending more and more to regard Transvasin as an indispensable adjuvant to treatment.

For Transvasin is composed of the esters of nicotinic, salicylic and p-aminobenzoic acids. These esters readily pass the skin barrier in therapeutic quantities, and so enable an effective concentration of drugs to be built up where they are needed.*

Transvasin not only induces vasodilation of the skin with a superficial erythema, but also brings about a deep hyperaemia of the underlying tissues. It is non-irritant and can be safely used on delicate skins.

It is now being widely prescribed, with successful clinical results. Since a very small quantity is sufficient for each application, the cost of treatment is extremely low.

**Therapeutische Umschau VIII, 1952, 10, 143.*

Salicylic acid tetrahydrofurfuryl-ester...	14%
Nicotinic acid ethyl-ester.....	2%
Nicotinic acid n-hexyl-ester.....	2%
p-Aminobenzoic acid ethyl-ester.....	2%
Water-miscible cream base ad	100%

Transvasin is available in 1 oz. tubes, basic N.H.S. price 2/6 plus P.T., and is not advertised to the public. Samples and literature will be gladly sent on application.

LLOYD-HAMOL LTD

11 Waterloo Place, London, S.W.1. Tel. WHItehall 8654/5/6

Transvasin is the registered trade mark of Lloyd-Hamol Ltd.

KOLANTYL

for more complete medical treatment of peptic ulcer

ANTISPASMODIC

To reduce ulcer pain and to delay stomach emptying, so assisting antacid action.

ANTACID

To neutralise excess acid. The antacid component of 'Kolantyl' is virtually ideal; rapid and prolonged in action, neither laxating nor constipating.

ANTILYSOZYME

To inhibit excess lysozyme, which is believed to be a factor in the aetiology of peptic ulcer.

DEMULCENT

To ensure ingredients adhere to mucosal surfaces and to assist in protecting the ulcer crater.

"... may be safely tried out under G.P. conditions with every prospect of a good result..."
Medical World (1955) 82: 379

Formula

Each tablet or 10 c.c. of Gel contains:

'Merbentyl' (diethylaminocarbethoxybicyclohexyl hydrochloride)	5 mg.
Dried Aluminium Hydroxide Gel	400 mg.
Heavy Magnesium Oxide	200 mg.
Sodium Lauryl Sulphate	25 mg.
Methylcellulose	100 mg.

Gel

Bottles of 12 fl. oz.

Tablets

Cartons of 48 and 240 tablets in roll packs of 12.

Dosage

1 to 2 tablets (2 to 4 teaspoonfuls of Gel) 3 or 4 times a day.

Merrell Research

'Kolantyl' and 'Merbentyl' are registered trade marks of the Wm. S. Merrell Co.

Distributed in Great Britain and Republic of Ireland by
RIKER LABORATORIES LTD.
LOUGHBOROUGH, LEICS.

between the UP

and the ABOUT

INFLUENZA and other debilitating illnesses are inevitably followed by a frustrating period of convalescence. Metatone* with its stimulating, appetite-promoting combination of vitamin B_1 with strychnine and mineral glycerophosphates is ideally suited for the rapid restoration of normal metabolic function.

FORMULA
Each fluid ounce of Metatone contains

Vitamin B_1	3 mg.
Calcium Glycerophosphate	4 gr.
Potassium Glycerophosphate	4 gr.
Sodium Glycerophosphate	2 gr.
Manganese Glycerophosphate	½ gr.
Strychnine Glycerophosphate	8/200 gr.

Available in bottles of 8, 16 and 80 fl. ozs.

METATONE

* *Trade Mark*

speeds the return to normal activity

PARKE, DAVIS & Co. Ltd., *(Inc. U.S.A.)* HOUNSLOW, MIDDLESEX. *Telephone: Hounslow 2361*

165

PRO-BANTHĪNE* IN ULCER HEALING

FIG. 1. *"But X-ray study at this time still revealed the ulcer niche."*

FIG. 2. *In ten weeks "the niche was no longer visible radiologically or gastroscopically."*

Clinical Report on Pro-Banthīne

The case-history below of ulcer on the gastric side of gastro-jejunal stoma reveals significantly the high potency in low dosage of the well-tolerated anti-cholinergic agent, Pro-Banthīne.

M. D., female, age 48, had a posterior gastro-jejunostomy fourteen years previously for duodenal ulcer. Nine months prior to her first visit severe intractable pain recurred and a subtotal gastrectomy was performed at another hospital. She remained well for a few months and then because of recurrence of severe pain and marked weight loss, she was referred for treatment. X-ray study revealed a large ulcer niche on the gastric side of the anastomosis. Antacids and sedatives gave no relief from pain. She was given 60 mg. of Pro-Banthīne four times a day and within seventy-two hours was able to sleep through the night for the first time in weeks. After two weeks of Pro-Banthīne treatment the patient felt completely well, but X-ray study at this time still revealed the ulcer niche (Fig. 1). After a further ten weeks' treatment the niche was no longer visible radiologically or gastroscopically (Fig. 2). In the five months prior to the report she was maintained on 30 mg. of Pro-Banthīne four times daily without any recurrence of symptoms.

Pro-Banthīne, containing 15 mg. Propantheline Bromide, is the safe and potent anti-cholinergic which efficiently controls and decreases gastro-intestinal hypermotility and excess acidity. It has proved highly efficient not only in peptic ulcer but also in pancreatitis, hypertrophic gastritis, diverticulitis, biliary dyskinesia, spastic colon and other conditions.

Pro-Banthīne is also available compounded with Phenobarbitone (15 mg.) for the treatment of peptic ulcer when complicated by mental stress and anxiety. Both products are available in bottles of 40, 100 and 1000 tablets. G. D. Searle and Co. Ltd., High Wycombe, Bucks. Telephone: High Wycombe 1770.

* *Registered Trade Mark*

SEARLE

PB : P97

*N 15

The interesting case of

THA NGE NA

"In this land of plenty, (Burma) imaginary fears against certain nutritious and essential articles of food, keep mothers and growing children on a practically starvation diet. Here is, therefore, one major cause of increased infant mortality, poor health, poor resistance against infectious diseases, poor development and retarded growth . . . Many mothers have brought infants to me who were in a critical and hopeless condition. They were at a loss when asked what they thought caused the ailment. 'Tha Nge Na' ("The disease which attacks babies") was all they could think of . . . I had to explain to them that if they cared to listen to some advice regarding a preventive diet, they would not have occasion to bring their infants in a critical condition, and that any physician, having rightly diagnosed the case, could effect the same wonderful results by following the right line of treatment".

The Journal of Tropical Paediatrics, 1955. Volume 1, Page 47.

A healthy Burmese boy enjoys his mid-day feed.
U.N.O. photograph

Doctors in many parts of the world will recognise, in this interesting Burmese case, a problem similar to their own. An obvious answer is to provide a nutritionally sound 'preventive' diet from the weaning age onwards. Farex is ideal for this purpose. In Farex a well-balanced ration of fat, carbohydrate and protein is ensured by mixed cereal flours which are pre-cooked for easy digestibility. Essential minerals and vitamins are added. In addition Farex may be given a variety of flavours including those locally familiar and trusted.

Minerals and Vitamins in Farex	
Iron	6mg. per oz.
Calcium	250 „ „ „
Phosphorous	190 „ „ „
Vitamin B_1	0·4 „ „ „
Vitamin B_2	0·5 „ „ „
Vitamin D	500 units per oz

FAREX
TRADE MARK

GLAXO

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX. BYRon 3434
Subsidiary Companies or Agents in most countries

for refreshing sleep and a fresh awakening

Effective against all types of insomnia not due to pain, CARBRITAL* provides a combination of pentobarbitone sodium, a rapid-acting barbiturate, with carbromal, a mild sedative. This combination ensures the speedy onset of sleep and gently sustains it throughout the night, with little or no depression the following day.

CARBRITAL

*Trade Mark

In bottles of 25 and 250 capsules each containing pentobarbitone sodium (1½ grs.) and carbromal (4 grs.)
Also as Carbrital Elixir.

Parke, Davis & Company, Ltd. *(Inc. U.S.A.)* · Hounslow · Middlesex · Telephone: Hounslow 2361

95

17

SMITH & NEPHEW

Armamentarium against tuberculosis

Wherever P.A.S. is indicated **THERAPAS** (calcium 4-benzamido-salicylate) may be used. It is better tolerated by the patient and has a slightly sweet, not unpleasant taste. THERAPAS is as effective as P.A.S. in delaying the emergence of streptomycin resistance. Its value in the treatment of genito-urinary tuberculosis is well established.

THERAZID is a convenient combination of 'Therapas' and 'Pycazide'. For domiciliary treatment in particular THERAZID is the drug of choice. Patients complaining of gastro-intestinal upset and monotony of dosage of P.A.S. and isoniazid therapy will be happier and more co-operative on THERAZID. Available as powder or cachets.

PYCAZIDE is the Smith & Nephew name for isoniazid. PYCAZIDE syrup (blackcurrant flavoured) is available to permit greater flexibility of dosage than is possible with PYCAZIDE tablets, and is particularly suitable in the treatment of children. One teaspoonful is approximately equivalent to 20 mg. of isoniazid.

P.A.S. and isoniazid are combined in **PYCAMISAN** cachets in five different strengths enabling "made to measure" dosage to be prescribed with the least waste of time and effort. PYCAMISAN cachets are practically tasteless and easy to swallow and their use offers distinct advantages in domiciliary treatment of tuberculosis.

'PARAMISAN SODIUM' is the sodium salt of P.A.S. (sodium aminosalicylate B.P.). It is recommended in the combined chemotherapy of all the forms of tuberculosis. It is rapidly absorbed, rapidly excreted, and of low toxicity.

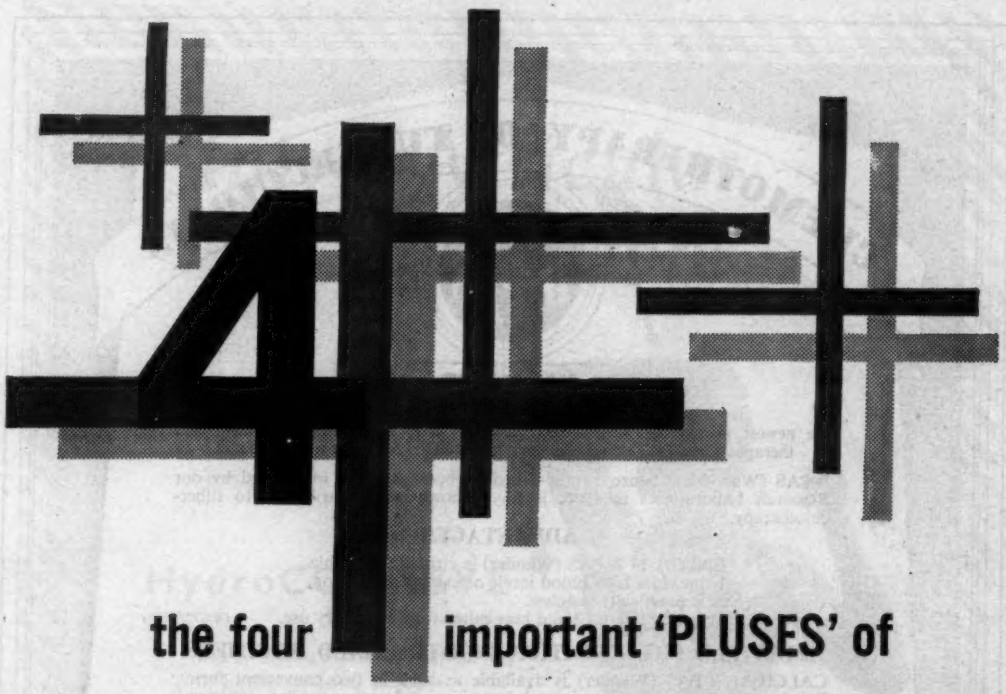
The cachet form of **'PARAMISAN SODIUM'** ('PASHETS') makes oral dosage possible without any unpleasant taste in the mouth. Twelve cachets provide a day's requirements of the drug.
'PARAMISAN SODIUM' is also available in tablet form and in ampoules for local injection.

As an alternative to isoniazid **NUPASAL-213** (o-hydroxybenzal isonicotinyl hydrazone) may be used in cases which have already exhibited toxicity to isoniazid, for the toxicity of NUPASAL-213 is virtually nil.

Dosages and presentations of any or all of these drugs will gladly be sent on request as space does not permit those details to be given in this advertisement.

S&N products

SMITH & NEPHEW PHARMACEUTICALS LTD · WELWYN GARDEN CITY · HERTS



the four important 'PLUSES' of

ACHROMYCIN*V

TETRACYCLINE WITH SODIUM METAPHOSPHATE *REGD TRADE MARK

What is the importance of ACHROMYCIN V to you? It provides the fullest possible benefits of true broad-spectrum therapy. It contains sodium metaphosphate which substantially aids in increasing absorption of the tetracycline, permitting

- **Swifter attainment of effective levels in the blood**
- **Higher 'peak' levels**
- **Longer lasting levels**
- **Effective control over the causative organisms**

These four important pluses are four very good reasons for prescribing ACHROMYCIN V, particularly for serious infections or where the infecting organisms show only borderline sensitivity to ACHROMYCIN.

Issued in capsules, each containing ACHROMYCIN tetracycline 250 mg. and sodium metaphosphate 380 mg. Bottles of 16, 100 and 1,000 capsules.

CYANAMID 1907 50 1957

LEDERLE LABORATORIES DIVISION

Cyanamid OF GREAT BRITAIN LTD., London, W.C.2

CHEMOTHERAPY OF TUBERCULOSIS

Calcium
B-PAS
WANDER

the newest proven modification of PAS for safe, acceptable, convenient and therapeutically reliable performance in combined regimens with Isoniazid.

B-PAS (Wander), 4-benzoylamino-2-hydroxybenzoate, first introduced by our Research Laboratories in 1948, is an acknowledged contribution to tuberculotherapy.

ADVANTAGES

CALCIUM B-PAS (Wander) is virtually insoluble.
It provides high blood levels of extended duration.
It is practically tasteless.
It is well tolerated and best suited for domiciliary use.

MULTIPLE PRESENTATION FOR COMBINED REGIMENS

CALCIUM B-PAS (Wander) is available as such in two convenient forms: Powder and Cachets. Content in each form is ranged so that the daily regimen is simplified. The 3.5 g. Powders taken with a draught of water or milk are especially acceptable. For combined regimens of B-PAS and INAH, 'B-PASINAH' Powders and Cachets according to preference supply the advantage of concurrent therapy in readily acceptable form which practically ensures the patient's co-operation in carrying out instructions.

PACKINGS

CALCIUM B-PAS WANDER

Powders: Tins of 150 and 400 x 3.5 g. envelopes
Cachets: „ „ 80 and 400 x 1.0 g.
Sodium B-PAS (Wander) also available in 1.5 g. Cachets

'B-PASINAH' (B-PAS plus Isoniazid)

Powders: Calcium B-PAS (Wander) 3.5 g.
Isoniazid ... ... 87.5 mg.
Tins of 150 and 400

Cachets: Calcium B-PAS (Wander) 1 g.
Isoniazid ... ... 25 mg.
Tins of 100 and 500

Full Abstracts from Literature on B-PAS, also details of institutional quantities and prices sent on request.

'PASINAH' Cachets of 1.5 g. Sodium PAS and 17, 25, 33 or 50 mg. Isoniazid also available.
Tins of 100 and 500

All Wander tuberculostatic products are obtainable from usual pharmacists or direct from

A. WANDER LIMITED

42 Upper Grosvenor Street, Grosvenor Square, London W.1

CANADA: A. Wander Ltd., Peterborough, Ontario. AUSTRALIA: A. Wander Ltd., Devonport, Tasmania. NEW ZEALAND: A. Wander Ltd., Christchurch. INDIA: Khatau Valabhdas & Co., Indian Globe Chambers, Fort Street, Fort, Bombay, 1. PAKISTAN: Grahams Trading Co. (Pakistan) Ltd., P.O. Box. 30, Karachi. CEYLON: A Baur & Co. Ltd., Colombo.

M 399

Intra-Articular Injections

HydroCORTISYL
INJECTABLE Hydrocortisone

2·5% sterile aqueous suspension of hydrocortisone acetate.

OR

PreCORTISYL
INJECTABLE Prednisolone

2·5% sterile aqueous suspension of prednisolone acetate.

PACKING

1 ml. and 5 ml. multidose bottles containing 25 mg. of either hormone per ml.

Reproduced by courtesy of the Trustees of the Tate Gallery, London.

ROUSSEL

LONDON N.W.10
LADbroke 6611

LS/72

Ultracortenol

with Bradosol

Cream

for eczemas
and other inflammatory, pruritic or
allergic skin disorders

The bactericide Bradosol prevents secondary infection which tends to develop during cortico-steroid therapy.

PROMPT RELIEF OF SYMPTOMS

PROLONGED DURATION OF ACTION

Tubes of 5g. containing 0.5% prednisolone trimethylacetate and 0.05% β-phenoxy-ethyl-dimethyl-dodecyl ammonium bromide in a specially formulated base.

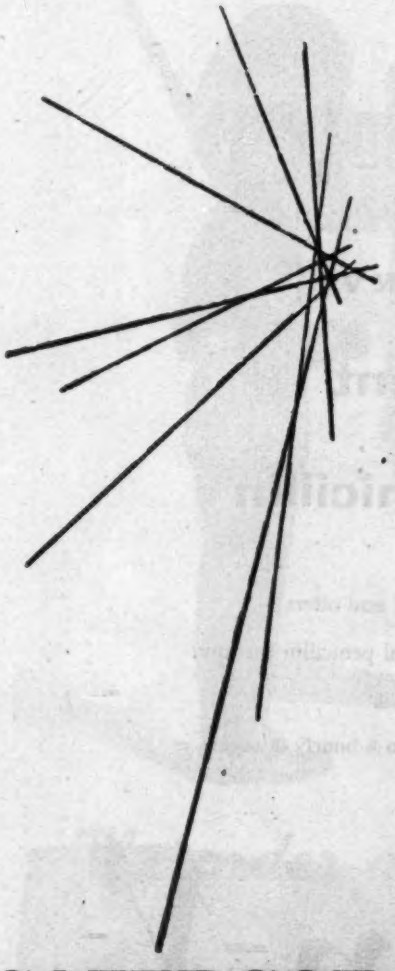
C I B A

'Ultracortenol' and 'Bradosol' are registered trade marks. Reg. use

CIBA LABORATORIES LIMITED · HORSHAM · SUSSEX

Telephone : Horsham 4321. Telegrams : Cibalabs, Horsham.

1/7



Migraine

and other headaches of vascular origin

are aborted in 80 per cent of cases by ORAL TREATMENT with

CAFERGOT

sugar-coated tablets

Ergotamine tartrate	1 mg.
Caffeine	100 mg.

Patients who experience nausea and vomiting early in the attack or who are unable to tolerate oral treatment, usually benefit from treatment with

CAFERGOT SUPPOSITORIES

Ergotamine tartrate	2 mg.
Caffeine	100 mg.
Isobutyl allylbarbituric acid	100 mg.
Total alkaloids of belladonna	0.25 mg.

Literature and samples are available on request

SANDOZ PRODUCTS LIMITED

Sandoz House, 23 Great Castle Street *London, W.1.*

Calcipen-V

CALCIUM-**PENICILLIN V**

the most efficient

oral penicillin

Calcipen-V is the calcium salt of **Penicillin V** and offers the following advantages in oral penicillin therapy:

rapid onset of action **reliable absorption**

sustained blood levels on 4 to 6 hourly dosage

Tablets of 60 mg. **Penicillin V** (as calcium salt). Bottles of 20, 100, 500.
Tablets of 120 m g. **Penicillin V** (as calcium salt). Bottles of 20, 100, 500.

Detailed literature will be gladly sent on request

BOOTS PURE DRUG CO. LTD., NOTTINGHAM, ENGLAND

Boots

3270

The order of the day...

'LANOXIN' *for maintenance therapy*

It never varies in potency.

It is taken each day, not intermittently.

Over-digitalisation quickly subsides because of rapid excretion.

'LANOXIN' BRAND *for unfailing control*

DIGOXIN

BURROUGHS WELLCOME & CO. *(The Wellcome Foundation Ltd.)* LONDON

To relieve joint pains and depression

The management of Influenza

IN THE ACUTE PHASE

'TERCIN'
TRADE MARK

Tablets containing 5 grains aspirin, 3 grains phenacetin and ¼ grain butobarbitone.

DOSE: One to three tablets as required.
Bottle of 200 tablets 4/10.

IN THE CONVALESCENT PHASE

'MULTIVITE'
TRADE MARK

Chocolate coated pellets of vitamin A 2500 i.u., vitamin B_1 0.5 mg. (160 i.u.), vitamin C 12.5 mg. (250 i.u.), vitamin D_2 6.25 µg. (250 i.u.).
DOSAGE: Adults: 2 pellets; Children: 1 pellet daily.
Bottle of 50 pellets 2/4.

'FERBELAN'
TRADE MARK

200 mg. green iron and ammonium citrate, 2 mg. vitamin B_1, 5 mg. nicotinamide, 0.5 mg. riboflavine in each teaspoonful.
DOSAGE: Adults: 1 or 2 tablespoonfuls daily.
Children: 1 or 2 teaspoonfuls daily.
Bottle of 4 fl. oz. 2/2.

To assist recovery when there is leeway to be made up in the nutritional status.

'LIVOGEN'
TRADE MARK

Each fluid ounce contains the therapeutic principles of 2 oz. fresh yeast and 4 oz. fresh liver together with added vitamin B_1 and nicotinic acid.
DOSAGE: 1 to 2 teaspoonfuls twice daily.
Bottle of 4 fl. oz. 4/-.

Basic N.H.S. Prices

Medical Department.
THE BRITISH DRUG HOUSES LTD. LONDON N.1

MECAMYLAMINE

A GANGLION-BLOCKING DRUG FOR TREATING HYPERTENSION

ARTHUR KITCHIN
M.B. Edin., M.R.C.P., M.R.C.P.E.
MEDICAL REGISTRAR

CLIFTON P. LOWTHER
M.B. Glasg., F.R.F.P.S.
SENIOR MEDICAL REGISTRAR

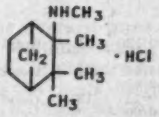
RICHARD W. D. TURNER
O.B.E., M.A., M.D. Camb., F.R.C.P., F.R.C.P.E.,
PHYSICIAN

WESTERN GENERAL HOSPITAL, EDINBURGH

THE value of ganglion-blocking drugs in the treatment of hypertension is now widely accepted. Oral hexamethonium has generally been abandoned owing to irregularity of absorption, the development of tolerance, and side-effects. Pentolinium by mouth has proved more acceptable owing to more regular absorption and longer duration of action, and in our experience the best results of pentolinium have been achieved with a combination of pentolinium and rauwolfia and occasionally, in patients with renal failure a combination of pentolinium, rauwolfia, and hydrallazine. Methonium and pentolinium share the disadvantage that both sympathetic and parasympathetic pathways are blocked, and only 10–20% of the dose is absorbed; and inequalities of absorption sometimes produce unpleasant side-effects.

It is now rarely necessary to use parenteral therapy in the long-term treatment of hypertension, and to be of interest any new drug which is not satisfactorily absorbed from the gastro-intestinal tract should have some outstanding property—e.g., selective action on the sympathetic nervous system. The ideal drug would be one which is completely soluble, is absorbed and excreted in a regular manner, and has a selective action on sympathetic ganglia. No such drug has yet been found; but mecamylamine is reputed to have certain advantages (Doyle et al. 1956, Freis and Wilson 1956, Moyer et al. 1956).

Mecamylamine (3 methylamino-isocamphane) is a secondary amine, whereas the methonium compounds, including pentolinium, are tertiary amines. Mecamylamine has the following structural formula:



Mecamylamine is so well absorbed that an effective dose is about the same by mouth and parenterally. There is no evidence of peripheral adrenergic blockade, and sympathomimetic drugs—e.g., noradrenaline and methedrine—are effective in decreasing the hypotensive effect.

The following clinical properties have been claimed by the manufacturers:

(1) The clinical effects are constantly reproducible in the same patient, because of complete oral absorption.
(2) The effect is gradual in onset and appears $^1/_2$–2 hours after oral administration.
(3) The duration of action is long, usually 6–12 hours.
(4) A smooth predictable response is obtained with minimal fluctuation of blood-pressure.
(5) It is the most potent oral ganglion-blocking agent available and is more than ninety times as active as hexamethonium.
(6) Mecamylamine may also be effective in patients who do not respond to hexamethonium or other ganglion-blocking agents.

The fact that mecamylamine is relatively more potent is of no particular importance. In the few patients in our series who have been treated with mecamylamine and pentolinium the hypotensive response has been similar but with a much smaller dose of mecamylamine. Opportunities to test the last claim are very infrequent because, in almost all hypertensive patients, the blood-pressure can be lowered, and the problem is rather whether the patient is suitable for treatment or whether lowering the pressure produces undesirable side-effects.

We have examined the first four of these claims in 36 hypertensive patients.

Method

Selection of Cases

36 consecutive cases of hypertension which, on assessment, were considered suitable for long-term drug treatment, were treated with mecamylamine by mouth in eighteen months. Usually such treatment was only undertaken where, in addition to high blood-pressure, there was objective evidence of hypertensive disease reflected in the retina or the electrocardiogram and the intention was to continue treatment for life. Impairment of renal function was not considered to be a contra-indication to treatment; nor was renal failure—i.e., retention of nitrogen—provided that the blood-urea level was not rising or above 100 mg. per 100 ml. A few cases were treated without such objective evidence of hypertensive disease; these were in young male patients with considerably raised blood-pressure.

That treatment was not advised for patients with relatively mild hypertension can be seen from the initial pressures recorded in the accompanying table.

Results are only considered in relation to the first 20 patients. Of these, 10 were treated for more than twelve months and 6 for more than nine months, and in 4 treatment was abandoned. 10 were males and 10 were females. The ages ranged from 33 to 61. All the patients were admitted to hospital for initial assessment. Secondary causes of hypertension were excluded in the usual ways, and the following factors were investigated: urine (including culture and specific gravity), creatinine clearance, phenolsulphonephthalein excretion, blood-urea nitrogen, intravenous pyelogram, electrocardiograms, chest radiography, detailed retinal examination in collaboration with an ophthalmologist, and, in 10 cases, renal biopsy. Evidence of associated atheromatous disease was sought as regards the brain, heart, and aorta. 3 patients had had cerebral vascular accidents in the past, and 2 angina pectoris. Electrocardiographic signs of left ventricular hypertrophy were present in 17. Renal function was impaired in 11, and of these 5 had nitrogen retention. Hypertensive changes in the retina were observed in 18, 10 of them having hæmorrhages or exudates and 4 papilloedema. The main clinical facts relating to each case are given in the table.

Measurement of Blood-pressure

In the ward resting and sleeping pressures were recorded in addition to occasional "run-throughs," by which is meant hourly recordings throughout the day.

Blood-pressure was measured always in the right arm. Pressures were recorded with the patient first supine and then erect. In each case the cuff was inflated over systolic pressure four times, only the reading obtained on the last inflation being recorded.

After discharge from hospital patients were seen first at a week's interval, then after a fortnight, and after this usually at monthly intervals unless the course of treatment dictated more frequent visits. At each follow-up visit the blood-pressure was recorded hourly for four or five hours, all readings being made by the same technician.

Administration of Mecamylamine

Initial stabilisation was done in hospital. The first dose was usually 2·5 mg. taken about eight-hourly each day. The dose was then increased by 2·5 mg. thrice daily at intervals of two days until the blood-pressure had been adequately lowered. The aim in most cases was to produce a normal blood-pressure, with standing diastolic pressures below 90 mm. Hg. The blood-pressure was lowered more cautiously in patients with evidence of myocardial ischæmia or cerebral atheroma. The dosage was further adjusted at subsequent visits to the clinic. If the pressure was above the level aimed at, the dose was increased by 2·5 mg. t.d.s.; if excessive postural hypotension or serious side-effects were reported, the dose was decreased.

This scheme of dosage was adopted on the basis of experiments in which single doses of mecamylamine were administered orally to untreated hypertensives and the lying and standing blood-pressures were followed throughout the following twelve hours. The following observations were made:

(1) There is a delay of one or two hours before the start of the hypotensive effect.

(2) The extent and duration of the hypotensive effect varies widely.

(3) The fall in blood-pressure takes place predominantly in the erect posture and is maximal from the third to the sixth hour.

(4) The blood-pressure does not return to standing basal values for at least twelve hours.

On the basis of these observations and others in which the pressures of patients stabilised on twice-daily dosage were followed for sixteen hours consecutively, it was thought preferable to give mecamylamine thrice daily.

Timing

It is reasonable to suppose that absorption will be more uniform if each dose is taken at the same time in relation to meals. With other drugs it has been found that smoother absorption results if the drug is taken just

CLINICAL DATA AND RESULTS OF TREATMENT OF 20 PATIENTS TREATED WITH MECAMYLAMINE WITH AND WITHOUT RAUWOLFIA

Case no.	Age (yr.)	Sex	Major symptom	Fundi	E.C.G.	Renal function	Blood-pressure (mm. Hg)						Remarks
							Initial	Resting	On mecamylamine		On mecamylamine and rauwolfia	Total mos.	Result (based on blood-pressure)	
									Stabilisation	Daily dose (mg.)				
1	58	M	C.V.A.	III	L.V.H.	R.F.	250/125	L. 190/115 S. 190/105	L. 230/110 S. 200/100	65	L. 220/110 S. 180/95	18	Fair	Regression of retinopathy and L.V.H., considerable tolerance
2	57	F	Visual	IV	L.V.H.	Imp	260/145	L. 200/130 S. 200/125	L. 165/90 S. 130/80	40	L. 165/95 S. 120/85	17	Good	Regression of retinopathy but not of L.V.H.
3	41	F	Headache	N	L.V.H.	Imp	230/125	L. 210/125 S. 175/110	L. 145/100 S. 125/95	30	L. 160/105 S. 125/90	17	Good	Regression of L.V.H.
4	60	M	L.V.F., A.P.	III	L.V.H.	R.F.	230/140	L. 210/125 S. 190/100	L. 200/100 S. 185/80	30	L. 195/90 S. 155/80	17	Good	No further L.V.F. or A.P., no regression of retinopathy or L.V.H.
5	46	M	C.V.A.	I	L.V.H.	N	230/120	L. 195/120 S. 180/120	L. 180/115 S. 155/110	30	—	(8)	Fair	Only moderate control sought, no regression of L.V.H., A.P. developed, treatment stopped
6	52	M	C.V.A.	III	L.V.H.	Imp	250/150	L. 170/130 S. 160/120	L. 150/105 S. 120/95	30	L. 145/105 S. 120/90	14	Good	Only moderate control sought, regression of retinopathy and L.V.H.
7	46	F	Dizziness	I	L.V.H.	N	230/130	L. 200/110 S. 190/100	L. 190/115 S. 170/100	40	L. 185/100 S. 150/90	14	Good	Regression of L.V.H.
8	57	F	C.C.F.	IV	L.V.H.	Imp	210/160	L. 170/135 S. 120/105	L. 160/110 S. 140/95	30	L. 150/105 S. 110/90	13	Good	Regression of retinopathy and L.V.H. followed previous adrenalectomy
9	47	F	Hæmaturia	IV	L.V.H.	Imp	260/160	L. 210/135 S. 190/130	L. 235/135 S. 170/110	97·5	L. 235/135 S. 170/110	(6)	Fair	Regression of retinopathy and L.V.H. depression of renal function, changed to pentolinium
10	52	M	Headache	II	L.V.H.	Imp	265/175	L. 230/165 S. 150/110	L. 235/135 S. 150/90	92·5	L. 190/120 S. 100/80	11	Good	Regression of L.V.H., tolerance developed
11	61	F	Visual	III	L.V.H.	R.F.	260/145	L. 230/115 S. 210/110	L. 210/115 S. 140/95	37·5	L. 185/95 S. 150/85	14	Good	Regression of retinopathy and L.V.H.
12	59	F	L.V.F.	IV	L.V.H.	N	290/160	L. 230/130 —	L. 220/115 S. 190/95	45	L. 170/75 S. 110/60	13	Good	Regression of retinopathy
13	36	M	C.V.A.	N	L.V.H.	R.F.	220/140	L. 210/135 S. 170/130	L. 190/120 S. 155/110	77·5	L. 195/125 S. 140/100	12	Fair	Nephrocalcinosis, no change in L.V.H., tolerance developed
14	56	F	Headache	II	L.V.H.	N	240/120	L. 190/120 S. 200/120	L. 165/90 S. 110/75	75	L. 185/100 S. 120/80	11	Good	Regression of L.V.H.
15	52	M	Headache	IV	L.V.H.	R.F.	230/150	L. 230/140 S. 240/140	L. 205/125 S. 105/70	55	L. 160/100 S. 110/80	10	Good	Regression of retinopathy
16	33	M	None	II	L.V.H.	R.F.	250/155	L. 190/155 S. 190/150	L. 170/125 S. 105/85	120	L. 175/125 S. 110/85	10	Good	Regression of retinopathy and L.V.H., considerable resistance
17	36	F	Lassitude	II	L.V.H.	N	210/130	L. 230/140 S. 220/130	L. 180/115 S. 110/85	80	L. 160/95 S. 110/70	10	Good	Regression of L.V.H.
18	51	M	Angina	IV	L.V.H.	N	230/140	L. 230/140 S. 215/140	L. 195/115 S. 150/105	15	L. 195/115 S. 150/105	(4)	Fair	Regression of retinopathy and L.V.H., poor cooperation, treatment stopped
19	52	F	Headache	III	Normal	N	260/130	L. 230/130 S. 230/120	L. 200/95 S. 180/85	67·5	L. 195/90 S. 170/85	9	Good	Regression of retinopathy
20	38	M	Lassitude	II	L.V.H.	N	225/150	L. 225/150 S. 190/140	L. 160/130 S. 155/120	45	— —	(3)	Fair	Regression of L.V.H., tolerance, intolerant of side-effects, treatment stopped

A.P., anginal pain. C.C.F., congestive cardiac failure. C.V.A., cerebrovascular accident. Imp, impaired renal function. L.V.F., left ventricular failure. L.V.H., left ventricular hypertrophy. N, normal. R.F., renal failure. Fundal classification—after Keith and Wagener. L, lying. S, standing. Rauwolfia was given as 'Rauwiloid' or reserpine. In the column headed total months parentheses indicate that treatment had to be either dropped or changed.

after a meal, and this should be the usual practice. It is not, of course, always possible for all the patients to keep to such a régime.

Some patients find that postural effects are most pronounced after the first dose in the morning, and in such cases we have advised that this dose should be smaller than the other two. In other patients the effects are most pronounced on first getting up; if this is the case, the last dose at night should be decreased.

Posture

Mecamylamine shares one of the disadvantages of other ganglion-blocking drugs in that it has no central action in lowering the blood-pressure, and often there is little fall in the lying position. It is therefore most important that full advantage should be taken of the beneficial effect of posture. This means that the horizontal position should be avoided as much as possible during the day. It is usually advised that the head of the bed should be raised on blocks at night; but, in our experience, the fall of pressure obtained by doing this is often slight.

Sensitivity

The dose required to achieve a satisfactory fall in blood-pressure varies widely, and some patients are highly resistant. Occasionally this may be due to the nature of the underlying disease or to secondary organic narrowing of the arterioles, but in other cases it seems to be due to varying sensitivity of the patient to the drug. In view of the advisability of increasing the dose gradually to avoid undue side-effects, reaching the correct level may be time-consuming. In such patients an intravenous injection may be the best means of demonstrating whether the patient is in fact sensitive but unusually tolerant or is resistant and incapable of responding. There should be no risk in doing this in favourable circumstances, because undue hypertension can be counteracted by raising the foot of the bed or, if necessary, by injecting a vasoconstrictor drug.

Results

A fall of blood-pressure has been taken as the sole criterion of the therapeutic effect of mecamylamine. As with other hypotensive agents, satisfactory control of the blood-pressure often leads to the alleviation of symptoms, the regression of hypertensive retinopathy or of the electrocardiographic pattern of left ventricular hypertrophy, and the relief of cardiac failure; but here, because of the short time for which most patients have been treated, reference is only made to control of the blood-pressure.

We have taken the average pressure recorded in the lying and standing positions during each visit to the clinic. Percentage falls in pressure are not a satisfactory method of expressing the result of treatment, because so much depends on the initial level. Obviously with a very high initial pressure—e.g., 260/150 mm. Hg—a percentage fall of 20 would signify a very different result from a similar drop in a patient with an initial pressure of 180/120 mm. Hg. A similar criticism can be made when a good or fairly good result is expressed in absolute figures. The following classification of results has therefore been adopted:

Since the aim has been to reduce the standing diastolic blood-pressure to normal levels (or nearly so), a good response is claimed if this is achieved.

If the pressure was considerably lowered but remained well above normal, a fairly good result is claimed.

If the blood-pressure could not be reduced, the result is classified as poor.

The 20 patients are considered from the point of view of the blood-pressure response and the development of tolerance, resistance, and side-effects.

Blood-pressure Response

The table shows, in addition to a summary of initial clinical data, the initial casual blood-pressure level before admission, the resting level after inpatient assessment, and those following stabilisation on mecamylamine. The resting blood-pressures consist in each case of the average of hourly blood-pressure recordings made throughout one day after admission to hospital. It will be seen that the dose of mecamylamine required for stabilisation was 30–120 mg. (average 60 mg.) daily.

The blood-pressures on the addition of reserpine 0·5–1·0 mg. daily or of rauwiloid 4·0–8·0 mg. daily are also given. In most cases the additional drug was given after a stable response to mecamylamine had been achieved, but in some cases the additional drug was given with mecamylamine from the beginning. The result claimed is based purely on the degree of control achieved over the blood-pressure. Good control was obtained in 14 patients and fair control in 6. However, as can be seen, fair control of the blood-pressure may have a good therapeutic effect.

In 13 of the 20 patients it was possible to assess whether a combination of mecamylamine and a rauwolfia preparation was better than mecamylamine alone. In 9 of these 13 cases the effect was beneficial in that a lower level of blood-pressure was reached or a smaller dose of mecamylamine was needed. Initially reserpine was used, but latterly rauwiloid because we have the impression that toxic effects with it are less common.

The reasons for failure to achieve a good result were considered to be as follows: 3 patients developed tolerance as regards the sympathetic action of mecamylamine and became intolerant to severe parasympathetic effects, and 1 other patient could not tolerate side-effects which other patients of more robust constitution might have tolerated. 1 patient developed œdema, which was related to a profound reduction in the glomerular filtration-rate, and 1 patient with previous symptoms of diffuse cerebral atheroma, in whom, therefore, only a moderate reduction in blood-pressure was sought in any case, developed angina pectoris. In the last 2 cases failure is attributable to the undesirable effects of reducing the blood-pressure and not to mecamylamine.

In summary, we consider that treatment was ineffective in 4 of the 20 patients because of undesirable effects directly attributable to mecamylamine.

Tolerance

Many patients develop a material degree of tolerance in the early stages, making periodic adjustments in dosage necessary. This was a persistent difficulty in only 4 cases of the present series. Tolerance is not often a serious problem but it emphasises the need for regular supervision as with other ganglion-blocking drugs.

Resistance

Though in many cases adequate falls in blood-pressure were accompanied by side-effects, in no case was it impossible to lower the pressure with mecamylamine. In case 16 a dosage of 50 mg. thrice daily was reached before a hypotensive response was obtained. That this apparent resistance was not due to failure of absorption was shown by giving mecamylamine intravenously. Renal biopsy showed that the patient had polycystic renal disease with definite arteriosclerosis but only slight impairment of renal function. Parasympathetic side-effects were minimal in this case.

Side-effects

The side-effects discussed here are those occurring with mecamylamine alone. We have the impression, from previous experience and from the occasional opportunity to compare the action of each drug in the same individual, that the action of mecamylamine may be smoother than that of pentolinium. However, we had previously found, as have others, that sometimes the combination of pentolinium with either reserpine or rauwiloid enabled a smaller dosage of pentolinium to be given to obtain the

same effect, and lowered the blood-pressure more smoothly and with fewer side-effects.

There is no doubt that mecamylamine is a potent drug for blocking transmission of sympathetic impulses, but what is chiefly required of a new ganglion-blocking agent is that it should have an isolated, or at least a more selective, action on the sympathetic nervous system. Unfortunately mecamylamine shares with methonium and pentolinium the disadvantage of blocking the parasympathetic impulses too, and to such a degree that many unpleasant symptoms follow; in fact, it often happens that these side-effects largely counterbalance the advantages of smoother absorption and action.

Symptoms from postural hypotension—i.e., the failure of normal reflex vasoconstriction—naturally depend on the degree of sympathetic blockade and not on the particular drug given. Their occurrence and severity are therefore irrelevant to any discussion on the relative merits of mecamylamine and other ganglion-blocking drugs. Likewise, with different drugs one would expect parasympathetic effects to differ in degree but not in quality. With mecamylamine they are at least as troublesome as with methonium or pentolinium and, in our experience, often more so, but this may be due to greater endeavour in recent years to obtain optimal control of the blood-pressure.

The side-effects observed were as follows:

Complaint	*No. of cases*
Constipation	19
Dry mouth and/or loss of taste	18
Blurring of vision	13
General malaise and fatigue	11
Diarrhœa	9
Stuffiness of nose	3
Difficulty in micturition	4
Impotence	(see text)

Constipation was no more of a problem than with pentolinium but was often troublesome and required constant vigilance. No more than twenty-four hours should be allowed to pass without taking remedial action. Since we abandoned methonium by mouth five years ago and fully realised the importance of prophylactic measures, none of our patients undergoing treatment for hypertension developed paralytic ileus. A regular aperient was usually required, and a satisfactory régime must be found for each patient. When distension is associated with constipation, oral neostigmine, which stimulates the parasympathetic nerve endings, should be tried in a dosage of 7·5–15·0 mg. b.d. It was found with pentolinium that constipation may improve from the addition of reserpine, and this may prove to be the case with mecamylamine. Recently 1 patient, not included in this series, developed severe distension with vomiting although an enema every other day produced a good motion.

Dryness of the mouth and impairment of taste were common and occurred in 18 of the 20 patients, being severe in 6. Oral pilocarpine (gr. $^1/_{10}$ t.d.s.) was sometimes an effective antidote but not always.

Blurring of vision from impairment of accommodation was common, especially in the early stages of treatment, and patients strongly objected to their inability to read. Pilocarpine drops (1–2%) should be tried first but are not always effective and are inconvenient to administer except in hospital. If the defect persists, slip-over lenses should be tried, with a view to ordering the appropriate spectacles if satisfactory.

Photophobia is another symptom about which complaint may be made, but it does not usually persist for long.

General malaise, fatigue, and weakness.—In our experience few patients with untreated hypertension feel ill; some come for advice because of unpleasant symptoms, visual disturbance, angina, or cardiac failure, and many because hypertension has been discovered during a routine examination, but usually such patients do not feel ill. By contrast, in our experience, most patients undergoing vigorous treatment for hypertension—i.e., optimal lowering of blood-pressure without undue side-effects—do not feel well and, if for any reason treatment has to be stopped, they feel much better. This is one reason why we recommend that treatment should not be advised unless there is objective evidence of hypertensive disease and unless, so far as can be judged, the prognosis without treatment is poor. With mecamylamine a vague and general feeling of malaise or fatigue is common. It was specifically mentioned by more than a third of the present patients and admitted on close questioning by others. In some cases it was related to the degree of associated sympathetic or parasympathetic effects, and in others the cause was obscure. Muscular weakness may be due to a mild anticholinergic or curare-like effect (Stone et al. 1956).

Diarrhœa, except as an occasional consequence of paralytic ileus or of overzealous treatment of constipation, was seldom a problem with methonium or with pentolinium; but with mecamylamine it was often troublesome and difficult to explain. Sometimes it was associated with mild distension and overactive bowel sounds, and sometimes with vomiting, but it was not associated with other manifestations of excessive sympathetic or parasympathetic blockade outside the gastro-intestinal tract. Possibly it was attributable to a direct irritant action on the bowel. In our experience it was not more likely to occur with too rapid an increase in dosage and might develop even with very gradual increments and respond to a slight decrease in dosage. Diarrhœa occurred in 9 of the 20 patients and consisted of 2–6 loose motions in twenty-four hours. It could not be attributed to aperients. It usually lasted from one to seven days, but in 4 cases there was a tendency for a single loose stool to accompany subsequent increases in dosage. In most patients the difficulty was overcome by persistence, with temporary reduction of dosage, or by the addition of the appropriate symptomatic treatment—e.g., chalk and opium mixture. The administration of oral neostigmine seemed definitely beneficial in 2 patients, possibly beneficial in 4, did not have any effect in 3, and did not aggravate the position in any. Since other workers do not seem to have experienced such a high incidence of diarrhœa, the effect may be due to the fact that we have given somewhat larger dosages of mecamylamine.

Stuffiness of the nose tended to pass off in time, and the temporary use of a 'Benzedrine' inhaler is justified.

Difficulty in micturition sometimes developed but was not serious and usually responded to oral prostigmine.

Impotence of various degrees in males sometimes caused embarrassment but tended to diminish in time. Not all the patients were questioned closely on this point.

Œdema.—One patient who had not in the past experienced any manifestations of cardiac failure developed severe peripheral œdema when a satisfactory fall in blood-pressure was produced, but she had no other signs which could be interpreted as indicating cardiac failure. It was found that her glomerular filtration-rate was greatly reduced and returned to normal with disappearance of the œdema when the blood-pressure was allowed to rise. That this was due solely to the fall in pressure and not to any toxic action of mecamylamine was shown by the reproduction of similar effects with pentolinium.

Discussion

Our objective in the treatment of these patients with important hypertensive disease was to lower the standing blood-pressure to as near normal levels as were compatible with freedom from undue side-effects. The aim of the present investigation was to discover whether mecamylamine in dosages tolerated by the patient can produce and maintain such a blood-pressure. We have

assumed that the sole beneficial effect has been from the lowering of the blood-pressure; and, so far as can be judged, with mecamylamine as with methonium and with pentolinium, relief of cerebral symptoms and reduction in cardiac failure, hypertensive retinopathy, and angina pectoris have been similar in kind and degree. Important side-effects from diminution of cerebral, coronary, and renal blood-flow may develop, but we have no knowledge of any other—e.g., chemical—action of mecamylamine.

Mecamylamine possesses the theoretical advantages of free solubility and complete absorption from the gut. As a result the hypotensive response, though variable from patient to patient, is reproducible in the same patient. Since its action lasts longer than that of pentolinium, administration three times daily is always, and twice daily sometimes, sufficient to maintain an effective reduction in blood-pressure for twenty-four hours in responsive patients.

In practice, however, the hypotensive effectiveness of mecamylamine is partly offset by side-effects, and few of our patients felt really well while taking mecamylamine; some experienced as many as nine side-effects. In contrast to the experience of Doyle et al. (1956) we observed persistent tolerance in 4 patients, and in most cases the dosage had to be gradually increased over the first year. Exact comparison between our series and that of Doyle et al. is impossible because these workers did not state what constituted a good result or the severity of the hypertension treated.

Though adequate lowering of the blood-pressure in the upright posture can be maintained with mecamylamine in most patients and undoubted beneficial effects follow, the severity and frequency of side-effects render mecamylamine far from satisfactory. The tendency for tolerance to develop obviates one of the main advantages which might be expected from a completely absorbable drug—i.e., longer intervals between follow-up visits.

We conclude that, whereas mecamylamine is probably the best of the ganglion-blocking drugs for treating hypertension, its advantages over pentolinium are not great, and the search for a drug with selective action on the sympathetic nervous system must continue.

Summary

Mecamylamine reduces hypertension by ganglion blockade and is well absorbed by mouth.

Of 36 patients considered suitable for long-term treatment with mecamylamine, 20 were followed up for periods up to eighteen months.

The hypotensive effect begins in one or two hours and is maximal from the third to the sixth hour.

Relief of subjective and objective manifestations of hypertensive disease was often observed; but, for the purpose of assessing the value of mecamylamine, the result was judged by its effect in reducing blood-pressure. This was considered to be good in 14 patients and fairly good in 6.

Reasons for failure to achieve a good result include resistance to mecamylamine and intolerance of parasympathetic side-effects or occasionally secondary effects from hypertension.

An appreciable degree of tolerance developed initially in many of the patients but persisted in only a few. Side-effects were troublesome in most cases, particularly from impairment of accommodation, dryness of the mouth, and constipation. In some patients diarrhœa was severe but did not persist.

9 of 13 patients benefited from a combination of mecamylamine with either serpasil or rauwiloid.

Mecamylamine is probably the best of the ganglion-blocking drugs at present available but is far from ideal.

Our thanks are due to Merck, Sharp, & Dohme Ltd. for generous supplies of their product 'Inversine' and to Miss N. Miller, research technician in the cardiac department of the hospital for recording many of the blood-pressures.

REFERENCES

Doyle, A. E., Murphy, E. A., Neilson, G. H. (1956) *Brit. med. J.* ii, 1209.
Freis, E. D., Wilson, I. M. (1956) *Arch. intern. Med.* 97, 551.
Moyer, J. H., Ford, R., Dennis, E., Caplovitz, C., Hershberger, R., Conner, P. K., Kinard, S., McConn, R. (1956) *Ibid*, 98, 187.
Stone, C. A., Torchiana, M. L., Navarro, A., Beyer, K. H. (1956) *J. Pharmacol.* 117, 169.

A TRIAL OF TWO ANTITUBERCULOUS DRUGS

DIPASIC AND NUPASAL-213

G. W. ALLAN
M.B. Glasg., M.R.C.P.E.
SENIOR REGISTRAR

W. MCNAUGHT
M.C., M.B. Glasg.
BACTERIOLOGIST

A. W. LEES
M.D., F.R.C.P.E., F.R.F.P.S., D.P.H.
CONSULTANT PHYSICIAN

RUCHILL HOSPITAL, GLASGOW

IT is generally agreed that the best way of using the standard antituberculous drugs—isoniazid, streptomycin, and *p*-aminosalicylic acid (P.A.S.)—is to give them daily, in combination, and for a long time. Isoniazid is very suitable for prolonged therapy because it is given orally and seldom causes toxic reactions, but neither streptomycin nor P.A.S. is an ideal companion for it. Streptomycin has to be given by intramuscular injection, and P.A.S., although given orally, is unpleasant to take and apt to upset the gastro-intestinal tract. Not infrequently, therefore, it is difficult to maintain therapy with a combination of standard drugs, and one or other of two new oral and relatively non-toxic preparations, 'Nupasal-213' and 'Dipasic,' have been widely used in substitution.

Nupasal-213 (*o*-hydroxybenzal isonicotinyl hydrazone), also known as 'Salizid,' and 'I.N.S.H.,' is a derivative of isoniazid, and (despite its name) is not related to P.A.S. In the body it is partly broken down into isoniazid; and, although it has been suggested (Steenken et al. 1954, Bavin et al. 1955) that the liberated isoniazid and the unconverted fraction of nupasal may have a combined action preventing the emergence of bacterial resistance to either substance, some have feared that this may not be so.

Dipasic (isonicotinic acid hydrazide-p-aminosalicylate) is a chemical combination of isoniazid and P.A.S., and doubts have been expressed about its efficacy. It has been argued that, if dipasic acts as a single substance, previous experience with antituberculous drug therapy suggests the early emergence of dipasic-resistant organisms; and that, if dipasic acts by breaking down in the body into isoniazid and P.A.S., the amount of P.A.S. which could be liberated from the recommended 600 mg. daily dose of dipasic would be too small for effective combined therapy, entailing the risk of organismal resistance to both isoniazid and P.A.S.

It therefore appeared to us worth while to conduct a controlled trial of nupasal-213 and of dipasic to get more information about their actions.

Material and Methods

All the patients, except those gravely ill, in whom a clinical diagnosis of active pulmonary tuberculosis was made for the first time on admission to hospital were allocated at random to one of the following four treatment schedules:

(1) Isoniazid 400 mg. daily plus P.A.S. 20 g. daily.
(2) Nupasal 2 g. daily plus P.A.S. 20 g. daily.
(3) Dipasic 1·2 g. daily.
(4) Nupasal 2 g. daily.

The customary dosage of nupasal is 1 g. daily, and of dipasic 600 mg. daily, but higher dosages of these drugs have been used without toxic effects; and, since the trial patients were under close observation, it was considered justifiable to double the usual dosages. All the patients who completed the trial were kept in hospital for six months and, except for the type of drug therapy, received identical treatment.

On admission, after three months' therapy, and after six months' therapy their weights and erythrocyte-sedimentation rates (E.S.R.) were recorded, a chest film was taken, and a specimen of respiratory secretions obtained by bronchial lavage was cultured. At the initial examination sputum, if available, was also cultured; failing that, a specimen of gastric washings was cultured. All the specimens were concentrated by Petroff's method (Mackie and McCartney 1953) and inoculated on to slopes

TABLE I—DISTRIBUTION OF PATIENTS BY SEX AND AGE

Treatment	No. of patients	Aged less than 55		Aged 55 or more	
		Male	Female	Male	Female
Isoniazid + P.A.S. ..	21	11	7	2	1
Nupasal + P.A.S. ..	21	10	8	2	1
Dipasic	22	11	8	2	1
Nupasal	22	12	8	1	1

of Löwenstein-Jensen's medium. Sensitivity tests were made on Löwenstein-Jensen slopes containing the following concentration of the trial drugs: isoniazid 5 μg. and 50 μg.; P.A.S. 2 μg. and 100 μg.; dipasic 1 μg. and 5 μg.; and nupasal 5 μg. and 10 μg.

Organisms were reported resistant when a growth of more than twenty colonies was present in each of the concentrations of the drug.

Results

92 patients were admitted to the trial. 6 did not complete it: 4 left hospital irregularly and were excluded, 1 patient died suddenly of coronary thrombosis, and 1 patient did not tolerate P.A.S. The results of treatment

TABLE II—AVERAGE INITIAL WEIGHT OF PATIENTS AND AVERAGE GAINS IN WEIGHT AT THREE AND SIX MONTHS

Treatment	No. of patients	Average weight at start (lb.)	Average gain in weight (lb.) at	
			3 mos.	6 mos.
Isoniazid + P.A.S. ..	21	113½	14·3	21·4
Nupasal + P.A.S.	21	111½	14·1	17·9
Dipasic	22	120½	17·6	22·7
Nupasal	22	120½	17·0	21·0

in the 86 patients who completed the six months' trial were as follows.

Age and Sex Distribution

Table I shows that the distribution of patients by sex and age (less than 55, 55 and more than 55) was much the same in the four treatment groups.

Clinical Response

Table II shows the average initial weight and the average weight gain at three months and at six months in the four treatment groups. There were no obvious differences.

Table III shows the distribution of normal (0–7 mm.), slightly raised (8–14 mm.), moderately raised (15–29 mm.), and much raised (30 mm. or more) E.S.R. in the four groups at the start, and the number and percentage of raised E.S.R. in the four groups which reverted to normal at three months and six months. At three months a greater percentage of raised E.S.R. had reverted to normal in the dipasic and nupasal groups; and at six

TABLE III—EFFECTS OF TREATMENT ON ERYTHROCYTE-SEDIMENTATION RATE

Treatment	No. of patients	E.S.R. at start (mm.)				No. of raised E.S.R.s which reverted to normal	
		0–7	8–14	15–29	>30	By 3 mos.	By 6 mos.
Isoniazid + P.A.S. ..	21	4	2	7	8	3 of 17	10 of 17
Nupasal + P.A.S. ..	21	3	2	4	12	5 of 18	8 of 18
Dipasic	22	3	4	8	7	9 of 19	10 of 19
Nupasal	22	6	1	8	7	8 of 16	10 of 16

months the percentages in all the groups were much the same.

Radiological Response

Clearing of lung zones.—The number of the conventional six lung zones affected by tuberculosis in each patient was noted at the beginning of therapy, after three months, and after six months. The total number of lung zones which had cleared in each of the treatment groups after three months' and after six months' therapy was thus estimated. The results are shown in table IV. It will be seen that the results are similar for each of the four treatment groups. A somewhat higher percentage of zones cleared in the nupasal and dipasic groups than in the other two.

Cavity closure.—Table V shows the total number of cavities noted in each of the groups at the start, and the

TABLE IV—CLEARING OF LUNG ZONES

Treatment	No. of patients	Zones involved at start	Zones cleared	
			By 3 mos.	By 6 mos.
Isoniazid + P.A.S.	21	76	13 (17·1%)	18 (23·8%)
Nupasal + P.A.S.	21	64	10 (15·6%)	17 (26·6%)
Dipasic	22	75	18 (24%)	24 (32%)
Nupasal	22	83	20 (24·1%)	30 (36·1%)

number and percentage of cavities closed at three months and at six months. It also shows the distribution of cavities by size in each group at the start. As it happened, large cavities (more than 2 inches in diameter) were present only in the groups on combined therapy; nevertheless a greater proportion of cavities closed in the isoniazid plus P.A.S. group (83·3%) and in the nupasal plus P.A.S. group (89·5%) than in the nupasal group (76·5%) and in the dipasic group (68·2%).

Bacteriology

Sputum conversion.—Table VI shows the number of patients with a positive sputum culture initially, at three months, and at six months. Of the 21 patients treated with isoniazid plus P.A.S. 16 had a positive culture at the start, 4 were positive at three months, and 2 were positive at six months. Of the 22 patients treated with Nupasal plus P.A.S. 16 had a positive culture at the start, 1 was positive at three months, and none was positive at six months. Of the 22 patients treated with dipasic 17 had a positive culture at the start, 9 were positive at three

TABLE V—EFFECT OF TREATMENT ON CAVITIES

Treatment	No. of patients	Start					3 mos.		6 mos.	
		Patients with cavities	No. of cavities	Size of cavities			Patients with cavities	No. of cavities	Patients with cavities	No. of cavities
				> 2in.	> 1 in. < 2 in.	< 1 in.				
Isoniazid + P.A.S.	21	11	18	3	5	10	8	10	3	3
Nupasal + P.A.S.	21	12	19	2	9	8	6	8	2	2
Dipasic	22	9	22	0	5	17	7	11	5	7
Nupasal	22	11	17	0	6	11	6	7	3	4

months, and 8 were positive at six months. Of the 22 patients treated with nupasal 16 had a positive culture at the start, 10 were positive at three months, and 3 were positive at six months. As regards sputum conversion, therefore, the dipasic group fared badly.

Drug resistance.—Table VII shows the pattern of resistance at three months and at six months to the four drugs tested. There were 4 positive cultures in the isoniazid plus P.A.S. group at three months and 2 positive cultures at six months; the organisms were sensitive to all four drugs in every case. There was 1 positive culture at three months in the nupasal plus P.A.S. group; the organisms were sensitive to all four drugs. There were no positive cultures at six months in the nupasal plus P.A.S. group. Of the 9 positive cultures at three months in the dipasic group 6 were resistant to one or more of the four drugs: 4 were resistant to both isoniazid and nupasal but sensitive to dipasic and P.A.S., 1 was resistant to isoniazid but not to nupasal, dipasic, or P.A.S., and 1 was resistant to nupasal but not to isoniazid, dipasic, or P.A.S. Of the 8 positive cultures at six months in this group 5 were resistant to isoniazid, 4 of the 5 were also resistant to nupasal but not to dipasic or P.A.S., and the other 1 was resistant to dipasic as well as isoniazid but not to nupasal or P.A.S. In 1 of these patients the initial sensitivities were not known; in the others the organisms were sensitive to all four drugs. Of the 10 positive cultures at three months in the nupasal group 5 were resistant to one or more of the four drugs: 3 were resistant to both isoniazid and nupasal but sensitive to dipasic and P.A.S., 1 was resistant to isoniazid but not to nupasal, dipasic, or P.A.S., and 1 was resistant to nupasal but not to isoniazid, dipasic, or P.A.S. In 4 of these patients the organisms had been shown to be fully sensitive at the start. There were 3 positive cultures at six months in the nupasal group, and all were resistant to isoniazid and to nupasal but sensitive to dipasic and P.A.S. In these 3 cases the organisms had been shown to be fully sensitive initially.

TABLE VI—SPUTUM CONVERSION

Treatment	No. of patients	No. positive		
		At start	At 3 mos.	At 6 mos.
Isoniazid + P.A.S.	21	16	4	2
Nupasal + P.A.S.	21	16	1	0
Dipasic	22	17	9	8
Nupasal	22	16	10	3

TABLE VII—DRUG RESISTANCE

Treatment	No. positive at 3 mos.	Resistant at 3 mos. to					No. positive at 6 mos.	Resistant at 6 mos. to				
		One or more drugs	Isoniazid	Nupasal	Dipasic	P.A.S.		One or more drugs	Isoniazid	Nupasal	Dipasic	P.A.S.
Isoniazid + P.A.S. ..	4	0	0	0	0	0	2	0	0	0	0	0
Nupasal + P.A.S. ..	1	0	0	0	0	0	0	..	..	..	..	..
Dipasic ..	9	6	5	5	0	0	8	5	5	4	1	0
Nupasal ..	10	5	4	4	0	0	3	3	3	3	0	0

Discussion

In the group treated with nupasal alone the organisms which became resistant to nupasal were almost invariably resistant to isoniazid, and in the dipasic group organisms which became resistant to isoniazid were almost invariably resistant to nupasal; such discrepancies as there were could well be due to unevenness of laboratory technique.

This parallel emergence of resistance to nupasal and isoniazid, and the fact that the combination of P.A.S. with nupasal increased the proportion of sputum conversions and prevented the emergence of nupasal and isoniazid resistance, suggest that nupasal owes its antituberculous activity entirely or almost entirely to the isoniazid liberated from it in the body.

Katz et al. (1954) successfully treated with nupasal cases in which isoniazid therapy had to be stopped because of neurotoxicity, and suggested that nupasal might prove useful in this way; but they substituted for the isoniazid an equal weight of nupasal. If nupasal depends for its activity on the amount of isoniazid liberated, this may have amounted to an indirect method of reducing the dose of isoniazid. In the present investigation there was no neurotoxicity either with the 2 g. dosage of nupasal or with the 400 mg. dosage of isoniazid; we have, however, observed the development of neurotoxicity in patients outside this series who were treated with the same dosages of these drugs. Vargas Jiménez (1956), using isoniazid alone, reported good clinical and radiological results even in cavitatory disease, and it will be noted that there was little to choose between the clinical and radiological results of nupasal alone and those of combined therapy—nupasal plus P.A.S., and isoniazid plus P.A.S. The advantage of combined therapy in preventing or postponing the emergence of bacteriological resistance was, however, once again demonstrated. It might be thought that, in cases of non-cavitatory disease, it would be possible to dispense with combined therapy, and it is therefore worth pointing out that the disease was of this type in one of the 3 nupasal-treated cases from which isoniazid and nupasal-resistant organisms were recovered at six months.

Dipasic proved disappointing in this series. The proportion of cavities closed was smaller than with the other drug régimes, and the bacteriological results were poor. Of 17 cases positive at the start of therapy 8 were still positive after six months, and in 5 of these 8 cases the bacilli were resistant to isoniazid. The fact that resistance to dipasic was demonstrated in only 1 of these 5 isoniazid-resistant cases suggests that in vitro dipasic acts as a chemical compound distinct from its constituent substances, but that in vivo its action is the same as, or similar to that of, isoniazid. If this is so, dipasic therapy is likely to prove disappointing in previously treated cases with organisms reported as isoniazid-resistant and dipasic-sensitive. In this trial there was no evidence of a P.A.S. action guarding against the development of isoniazid resistance; nor, on the other hand, was there any evidence of emerging resistance to P.A.S. Perhaps the explanation for both these findings is that, if P.A.S. is split off from dipasic in the body at all, the amount is insignificant.

Summary

A trial was made of four antituberculous drug régimes—isoniazid 400 mg. daily plus P.A.S. 20 g. daily, nupasal-213 2 g. daily plus P.A.S. 20 g. daily, nupasal-213 2 g. daily, and dipasic 1·2 daily.

The clinical response and degree of resolution of non-cavitatory disease were comparable in all the groups. Cavity closure at six months, however, was less common in the nupasal group (76·5%), and still less common in the dipasic group (68·2%), than in the isoniazid plus P.A.S. group (83·3%) or in the nupasal plus P.A.S. group (89·5%).

Bacteriological results demonstrating a parallel emergence of isoniazid and nupasal resistance in the groups treated with single drug therapy, and the protective effect of supplementing nupasal therapy with P.A.S., suggest that nupasal is equivalent in effect to isoniazid. Dipasic therapy was inferior to therapy with nupasal alone (and thus presumably to isoniazid alone) in achieving sputum conversion, and gave rise to the emergence of isoniazid-resistant organisms. There was no evidence that, if P.A.S. is split off from the dipasic in the body, a

sufficient amount is formed to prevent isoniazid resistance or to give rise to P.A.S. resistance.

REFERENCES

Bavin, E. M., Kay, E., Seymour, D. E. (1955) *Lancet*, i, 303.
Katz, S., McCormick, G. F., Storey, P. B., de Leon, A., Romansky, M. J., Marshall, E. E. (1954) Transactions of the 13th Conference on the Chemotherapy of Tuberculosis. Washington; p. 374.
Mackie, T. J., McCartney, J. E. (1953) Handbook of Practical Bacteriology. 9th ed., Edinburgh; p. 404.
Steenken, W. jun., Wolinsky, E., Montalbine, V. (1954) *Proc. Soc. exp. Biol., N.Y.* 87, 245.
Vargas Jiménez, F. (1956) *Amer. Rev. Tuberc.* 74, 903.

SENSITIVITY OF MYCOBACTERIUM TUBERCULOSIS TO PARA-AMINOSALICYLIC ACID, ISONIAZID, AND THE P.A.S. SALT OF ISONIAZID

J. M. DUNBAR
M.D., B.Sc. St. And.
LECTURER IN BACTERIOLOGY, QUEEN'S COLLEGE, UNIVERSITY OF ST. ANDREWS

R. T. RITCHIE
M.B. Edin., M.R.C.P.E.
ASSISTANT CHEST PHYSICIAN, DUNDEE AREA

THE *p*-aminosalicylic-acid (P.A.S.) salt of isoniazid was introduced in 1953 and shown by Smith and Wiederkehr (1953), Aufdermaur and Brodhage (1953), and Brodhage (1954) to possess bacteriostatic action against *Mycobacterium tuberculosis*. Smith and Wiederkehr (1953), Brodhage (1954), and Clegg (1955) have stated that it is actively bacteriostatic against strains of bacilli which are known to be resistant to isoniazid (I.N.H.) or to P.A.S., or to both. The active substance (' Dipasic ') henceforth referred to as salt P.A.S. : I.N.H. is stated to be an addition compound of I.N.H. and P.A.S., combined in the ratio of 1 : 1.

In view of the encouraging results obtained by other workers we decided to test freshly isolated strains of *M. tuberculosis* against the salt P.A.S. : I.N.H. and to consider using the drug if any of the strains were found to be sensitive to it and resistant to P.A.S. or to I.N.H. Unfortunately, 3 patients had received salt P.A.S. : I.N.H. before cultures were obtained.

Method

Strains of *M. tuberculosis* from 16 patients known to harbour organisms resistant to I.N.H. were tested against the salt P.A.S. : I.N.H. The sensitivity tests for I.N.H. were made by the technique recommended by the Medical Research Council (1953). Solid medium was also used in testing the sensitivity to P.A.S., the salt P.A.S. : I.N.H., and the combination of P.A.S. + I.N.H. in the same medium.

The following concentrations of drugs in Löwenstein-Jensen medium were used: I.N.H. 1 and 5 μg. per ml.; P.A.S. 2 and 10 μg. per ml.; P.A.S. 2 μg. per ml. + I.N.H. 1 μg. per ml. in the same slope; P.A.S. 10 μg. per ml. + I.N.H. 5 μg. per ml. in the same slope; and salt P.A.S. : I.N.H. 1 and 5 μg. per ml. Clegg (1955) used 0·2, 1, 5, and 50 μg. per ml. of salt P.A.S. : I.N.H. in L–J slopes; and, since he considered growth at 5 μg. per ml. to indicate resistance, 1 and 5 μg. per ml. were selected.

Difficulty was experienced in dissolving the salt P.A.S. : I.N.H. in water; so weak alkali was used. 0·2 g. of the powder was added to 100 ml. of 1/1000 *N* NaOH, and this was incubated at 37°C with frequent shaking until all the powder was dissolved (J. W. Clegg, personal communication). The solution was sterilised by Seitz filtration, and the filtrate was used as a stock for the preparation of dilutions of the drug in L–J medium.

RESULTS OF SENSITIVITY TESTS ON 16 STRAINS OF *M. tuberculosis* AGAINST P.A.S., I.N.H., COMBINED P.A.S. + I.N.H. AND SALT P.A.S. : I.N.H.

Strain no.	P.A.S.	I.N.H.	P.A.S. + I.N.H.	Salt P.A.S. : I.N.H.
1	R	R	R	R
2	R	R	R	R
3	R	R	R	R
4	R	R	R	R
5	R	R	R	R
6	R	R	R	R
7	R	R	PR	R
8*	R	R	PR	R
9	PR	R	PR	R
10*	R	R	PR	PR
11	R	PR	PR	R
12	S	R	S	PR
13*	S	R	S	PR
14	S	R	S	PR
15	S	R	S	S
16	R	R	S	S
Control H37Rv	S	S	S	S

PR, partially resistant. R, resistant. S, sensitive.
* These patients were treated with the salt P.A.S. : I.N.H. before cultures were obtained.

Results

The H37Rv strain was included as a control in each batch of sensitivity tests, and the cultures were examined after four weeks' incubation at 37°C.

Moderate or heavy growth on the L–J slope containing the higher concentration of drug or drugs in combination was regarded as indicating resistance; moderate growth at the lower concentration and no growth at the higher concentration was regarded as indicating partial resistance; and no growth at both concentrations was regarded as indicating sensitivity.

The results of the sensitivity tests are shown in the accompanying table.

15 strains were resistant and 1 was partially resistant to I.N.H.; 11 were resistant, 1 was partially resistant, and 4 were sensitive to P.A.S.

6 strains (nos. 1–6) were resistant to P.A.S., I.N.H., the combination P.A.S. + I.N.H., and the salt P.A.S. : I.N.H.

5 strains (nos. 7–11) were partially resistant to the combination P.A.S. + I.N.H., and 4 of these were resistant to the salt P.A.S. : I.N.H., and only 1 was partially resistant.

4 strains (nos. 12–15) were sensitive to P.A.S., resistant to I.N.H., and sensitive to the combination P.A.S. : I.N.H., and 3 of them were partially resistant to the salt P.A.S. : I.N.H., only 1 being sensitive to it.

Only 1 strain (no. 16) was resistant to P.A.S. and to I.N.H. but sensitive to the combination P.A.S. + I.N.H. and to the salt P.A.S. : I.N.H.

4 strains (nos. 7, 8, 10, and 16) were resistant to both P.A.S. and I.N.H., 3 being partially resistant to the combination P.A.S. + I.N.H., and the other (no. 16) sensitive to it.

Discussion

The results of the sensitivity tests on 16 strains of *M. tuberculosis* indicate that in most cases, once resistance to I.N.H. has developed, the organisms are also resistant to the salt P.A.S. : I.N.H. This is in agreement with the findings of Tinne (1956) but conflicts with those of Clegg (1955).

Those organisms which are sensitive to P.A.S. though resistant to I.N.H. are, as would be expected, sensitive to the combination P.A.S. + I.N.H., but they are partially resistant to the salt P.A.S. : I.N.H. The sensitivity tests on 7 strains reported by Brodhage (1954) seem to support this: of his 5 strains resistant to I.N.H. 10 μg. or more per ml., 2 were resistant to the salt P.A.S. : I.N.H. at 5 μg. per ml., 2 were partially resistant at 1 μg. per ml., and only 1 was sensitive. These findings suggest that the P.A.S. fraction of the salt P.A.S. : I.N.H. does not have any striking effect in vitro. This requires further confirmation from in-vivo studies, and an attempt is being

made to study the blood and urine levels obtained from the P.A.S. fraction of the salt P.A.S. : I.N.H.

The results of the sensitivity tests to the combination P.A.S. + I.N.H. suggest that, even in the cases of 4 strains resistant to both P.A.S. and I.N.H. when tested individually in vitro, there is some augmentation of effect when in combination.

Only 1 strain was resistant to both P.A.S. and I.N.H. and yet sensitive to the salt P.A.S. : I.N.H. and to the combination P.A.S. + I.N.H. The significance of this is unknown.

Summary

Strains of *M. tuberculosis* isolated from 16 cases of pulmonary tuberculosis known to harbour I.N.H.-resistant organisms were tested in vitro against concentrations of P.A.S. (2 and 10 μg. per ml.), a combination of P.A.S. (2 or 10 μg. per ml.) + I.N.H. (1 or 5 μg. per ml.) in the same Löwenstein-Jensen slope, and the salt P.A.S. : I.N.H. (1 and 5 μg. per ml.). Of these strains only 2 were sensitive to the salt P.A.S. : I.N.H., but 5 were sensitive to the combination P.A.S. + I.N.H.

It is concluded that resistance to the salt P.A.S. : I.N.H. closely mirrors that to isoniazid.

We are grateful to Prof. W. T. Tulloch, of Queen's College, University of St. Andrews, and Dr. R. N. Johnston and Dr. D. H. Smith, of Ashludie Chest Hospital, Monifieth, for facilities; to Mr. D. Allan, A.I.M.L.T., for technical assistance; and to Messrs. Bengue for the supply of the salt P.A.S. : I.N.H. (dipasic) used in the sensitivity tests.

ADDENDUM

Since this report was submitted, Walker et al. (1957) show, from clinical and bacteriological studies, a close correlation between the degree of resistance to dipasic and the resistances to P.A.S. or to I.N.H., whichever is the lower. They conclude that treatment with dipasic should be regarded as equivalent to treatment with I.N.H. alone.

REFERENCES

Aufdermaur, M., Brodhage, H. (1953) *Praxis*, **42**, 885.
Brodhage, H. (1954) *Science*, **120**, 998.
Clegg, J. W. (1955) *Brit. med. J.* ii, 1004.
Medical Research Council (1953) *Lancet*, ii, 213.
Smith, A. E. W., Wiederkehr, F. X. (1953) *Praxis*, **42**, 884.
Tinne, J. E. (1956) *Lancet*, ii, 252.
Walker, W. C., Hay, D., Stewart, S. M., Crofton, J. W. (1957) *Tubercle*, **38**, 238.

CARCINOMA OF THE ŒSOPHAGUS

THE CASE FOR SURGICAL EXCISION

J. LEIGH COLLIS

M.D., B.Sc. Birm., F.R.C.S.

SURGEON, QUEEN ELIZABETH HOSPITAL, BIRMINGHAM

THE outstanding long-term success of Torek's (1913) original resection for œsophageal carcinoma had a profound effect on medical opinion. It gave rise to the firm view that good late results were to be expected, and that the only problem was the reduction of immediate operative mortality. Follow-up results now available are certainly not so good as had been hoped. This has given rise to a tendency in some quarters to discredit radical surgical treatment and to suggest that either surgical palliation or radiotherapy should be used.

The evidence for surgical excision is presented here.

Radiotherapy

In an excellent review of the results obtained from radiotherapy at the Royal Marsden Hospital Smithers (1957) describes his experience with the new super-voltage machines installed in 1936. He restates the hopelessness of the position without treatment and illustrates this from experience of 65 patients who had no treatment and who were all dead in less than two years. Radiotherapy was used for 229 patients, of whom 20 survived more than two years. This represents only 9% of the total, and it is perhaps unfortunate that Smithers compares the result with a short series of 20 cases treated surgically.

Smithers aptly observes that we should judge the value of a treatment by the best that has been achieved. In view of the soundness of this observation I shall not dwell on less satisfactory experiences. It is also to be expected that the better radiotherapy equipment available in recent years will be still further improved. Nevertheless Köhler (1951) could find only 3% of his patients alive after two years. A similar figure was reported by Krebs et al. (1949); but, when only the upper end of the œsophagus was considered, the number of two-year survivors increased to 10%. Luppinger (1936) found only 1% alive after two years.

Mustard and Ibberson (1956) have recently reported a series of cases treated with supervoltage radiotherapy at the Toronto General Hospital, and their results are very similar to those of Smithers. Of 125 patients given this treatment they found 10 (8%) surviving two years. As Smithers did, they compare the radiotherapy series with a rather unfortunate surgical experience, but, even though the operative mortality was 40%, 15% of the patients survived two years.

TABLE I—FIVE-YEAR SURVIVORS

Site	Surgery	Radiotherapy
Upper	2	33
Middle	7	15
Lower	65	13

Smithers (1957) drew up this table by collecting all recorded instances of patients surviving five years.

From these reports it seems that radiotherapy can prolong life but only to the extent of allowing rather less than 10% of the patients to survive beyond two years. Although this may not be very encouraging, there are better sides to the picture: most workers are convinced that the palliation which they can achieve is considerable; and the best results from radiotherapy are produced with growths in the upper part of the œsophagus. This becomes particularly important when it is considered in association with the finding of the worst late surgical results in the same area. Smithers (1957) has brought strong evidence in support of this by collecting all the published instances of patients who have survived five years (table I). No statistical conclusions can be drawn from these figures, because the numbers in the groups from which the survivors came are unknown. Presumably it is more accurate to compare different groups treated by radiotherapy than to compare radiotherapy groups with surgical groups. On this basis radiotherapy is much more effective when used for growths at the upper end of the œsophagus than for growths in the middle and lower areas. Similarly surgery gives its best results with growths at the lower end of the œsophagus.

A third encouraging aspect is the necropsy findings in patients who have received radiotherapy for œsophageal growths. In such cases it is often difficult to demonstrate any remaining malignant tissue. 4 such cases published by Watson and Brown (1951) strongly confirm the power of radiotherapy to control cancer even when it is so deeply placed as in the middle or the lower œsophagus.

Surgery

Surgery has two potential handicaps in the initial operative mortality and the fact that surgery is not universally applicable. The first is likely always to remain to some extent, although continued effort has shown that operative mortality can be reduced very considerably.

The consistently good results reported by Sweet (1954) are well known. Over the three-year period 1950–52 his

operative mortality for the middle of the œsophagus was 25% and for the lower end 7%. Even more remarkable is how near to this figure are his results for his whole series. There is little doubt that many centres have unpublished series which show an operative mortality approximating to these figures. Certainly the results of Garlock (1947) of New York, K. Nakayama in Tokyo (personal communication), and Wu and Loucks (1951) of Peking seem well up to this standard, and I hope to show that my results are similar.

As regards the proportion of patients for whom resection cannot be done, the position is much less unsatisfactory than with carcinoma of the lung. This is because both the percentage of cases which prove to be inoperable is lower and palliative surgery is more helpful. The relatively satisfactory palliative methods available may explain to some extent the wide variation in the proportion of cases treated by resection in published series: Allison and Borrie (1949) 28%, Humphreys and Moore (1953) 33%, Parker and Jenkins (1955) 20%, and MacManus et al. (1956) 50%. Most writers are much more consistent in the resectability-rate of those explored; all those cited above gave 60–75%.

Sweet (1954) states that in 1950–52 he saw 83 patients and operated on 74 of them with 60 resections. This means that 67% of those seen had resections and 80% of those operated on had a resection.

TABLE II—ANALYSIS OF 336 CASES ADMITTED WITH CARCINOMA OF ŒSOPHAGUS AND CARDIA, 1947–1956

Operation	No. of patients
Radical resection	150 (44%)
Exploration	62 (19%)
Palliative	124 (37%)

From these figures it will be seen that 44% of the entire series were treated by surgical excision of the growth. It is also to be noted that 70% of those patients in whom an exploration was made had their growths removed.

Follow-up

In reviewing the published follow-up figures special attention has been paid to the percentage of patients who survived two years from the date of their operation. In addition all figures have been expressed as the percentage of patients who survived the operation because, if this is done, all the series are more readily comparable.

Sweet (1954) found that 26% of his patients with mid-thoracic growths and 28% of those with growths at the lower end survived two years. When only completely operable cases were considered, 63% of patients with growths at the lower end of the œsophagus survived two years and 34% survived five years. These last figures do not seem to have much practical application, and it is best to keep to the two-year survival. Of the patients of Allison and Borrie (1949) 33%; of the patients of Humphreys and Moore (1953) 37%; and of the patients of Mustard and Ibberson (1956) 25% were still alive two years after their operation.

From these reports considerable agreement can be reached about the chance of surviving two years after a successful surgical resection. In most of these series many cases were included in which the growths were advanced and might not have been considered operable by strict standards. However, even when all these are included, a third of the patients can expect to be alive at the end of two years, whether the growth is in the middle, or at the lower end, of the œsophagus, and in spite of the less favourable prognosis for the middle of the œsophagus after five years. A further point of importance is brought out by Sweet (1954), who finds no difference in the follow-up whether the growths are squamous-celled or adenocarcinomata.

Present Series

Table II shows that 44% of the patients were treated by surgical excision of the growth. It is also to be noted that 70% of those patients in whom an exploration was made had their growths removed.

TABLE III—ANALYSIS OF OPERATIVE MORTALITY

Cases 1–50	Mortality 52%
Cases 51–150	Mortality 14%

Last 100 cases:	*Total*	*Deaths*	*Mortality*
Upper	2	1	
Mid. 1	18	4	22%
Mid. 2	29	6	21%
Lower	51	3	6%

The mortality in the first 50 cases was very high, and the way it has been reduced in the last 100 cases is striking evidence of the desirability of benefiting from accumulated experience.

The broad principle which directed the type of treatment which should be used in this personal series of 336 patients was to operate whenever there seemed a reasonable chance of being able to remove the growth. Good palliation was achieved by œsophagoscopy and the introduction of a specially designed large-sized Souttar tube. For this reason cases with hepatic or other distant secondaries have not been explored. The same applies to cases where involvement of the carina was found at bronchoscopy. In all cases the object was to send the patient out of hospital with his swallowing improved. By-pass operations were only used for irremovable growths at the cardia. In the case of other growths found inoperable at thoracotomy œsophagoscopy was done with the chest open, and a large Souttar-type tube was passed through under direct vision. In any case explored the growth was removed if possible, although in a large proportion the growths might not strictly have been classed as operable if total eradication of the malignant tissue was the object. This line was taken because of the firm belief that patients have a greater sense of well being when the primary growth is eradicated. It is felt that this view is clearly substantiated in the follow-up period, especially by the greater ease with which such patients gain weight. In spite of this the benefit has not been considered great enough to make it a practice to operate on patients who already have distant secondaries.

TABLE IV—ANALYSIS OF CAUSES OF DEATH IN 40 OPERATIVE DEATHS

Cause of death	First 50 cases	Last 100 cases
Suture-line leak	12	1
Local sepsis	1	3
Bronchitis	6	2
Cardiac	5	3
Hypotension	..	2
Carotid thrombosis	1	..
Tracheotomy	..	1
Pleural effusion	..	1
Hæmopericardium	..	1
Doubtful	1	..
Total	26	14

Listed here are the main causes of death in the postoperative period. As between the two series there has been a striking reduction in the amount of trouble with the suture-line area and a smaller reduction in deaths from pulmonary complications.

It has been a general rule that growths at the upper end of the œsophagus have not been treated surgically. They have either been given deep X-ray therapy alone or have had this treatment after the introduction of a large Souttar-type tube. These various reasons explain the apparently rather large group of 124 patients treated palliatively.

Operative Mortality

Table III shows that the mortality in the first 50 cases was very high, and the way it has been reduced in the last 100 cases is striking evidence of the desirability of learning from accumulated experience.

The figures of operative mortality refer only to those cases in which the growth was removed and would be considerably lower if all explorations were included. In the first 50 cases done the mortality was alarmingly high,

but considerable improvement was effected in the next 100 cases. The overall mortality for these patients was 14%, with the usually experienced smaller mortality for growths at the lower end and cardia (6%). The growths in the middle part of the œsophagus are divided into two groups: Mid. 1 includes those cases in which the upper margin of the growth was at the level of the middle of the arch of the aorta or above; and Mid. 2 includes all growths below this but not within the last two inches of the lower end of the œsophagus. Of the 47 patients in these two groups 10 died, giving a mortality of just over 20%.

Causes of Death

Table IV shows the main causes of death in the post-operative period. As between the two series there was a striking reduction in the amount of trouble with the suture-line area and a smaller reduction in deaths from pulmonary complications.

TABLE V—SURVIVAL OF PATIENTS BY TREATMENT

Treatment	Total	Survival (months) -		
		0–12	12–24	24 +
No operation	199	189	10	0
Gastrostomy	83	73	10	0
Souttar's tube ..	14	14	0	0
Total	296	276 (93%)	20 (7%)	0
Deep X rays	99	82 (83%)	16 (16%)	1 (1%)

These results are taken from the Annual Cancer Report of the United Birmingham Hospitals, vol. 1, 1953, and deals with the period 1936–49.

The table compares the causes of death in the first 50 patients with those in the last 100. The one case of suture-line leak in the last 100 was an upper-end growth with a suture line in the neck. The difference between the two groups might be simplified by saying that deaths from suture-line leak have now been excluded, and thereby a third of the mortality has gone. The remaining causes of death have been halved, the resulting mortality being reduced to less than a third of what might be expected from earlier experience. The improvement in suture-line healing has been effected by extreme local care and by closing the mediastinum over the œsophagus and the stomach. When the original mediastinal pleura is not available, the posterior surface of the lung is used to effect this closure. The use of 40-gauge wire has been helpful in obtaining good suture-line healing.

The reduction in mortality from other causes has been obtained by attention to a variety of other factors which really amount to the most extreme care on the post-operative management. The reduction in deaths from pulmonary complications is attributed to a large extent to the practice of doing a tracheotomy in any case where coughing is difficult and before the patient's condition becomes critical. It is only fair to add that much credit for this overall reduction is due to the anæsthetist, Dr. G. A. Rawlins, who has officiated in all but a very few of these cases.

TABLE VI—SURVIVALS OF PATIENTS OPERATED ON BEFORE DECEMBER, 1954

Site of cancer	No. of cases	Survival 2 years +	2-year survival-rate
Upper	2	1	50%
Mid. 1	14	4	28%
Mid. 2	20	7	35%
Lower	36	12	33%
Total ..	72	24	33%

The 72 patients who survived surgical excision before December, 1954, have been analysed. It is to be noted that approximately a third of all cases with growths in the middle and lower œsophagus survived beyond the two-year stage. There has been 100% follow-up.

Follow-up

The survival periods of the patients not treated surgically have not been analysed separately, because the overall figures of the United Birmingham Hospital are available for this purpose. These include many of the cases in the present series.

The results shown in table V are taken from the Annual Cancer Report of the United Birmingham Hospitals, vol. I, 1953, and are for 1936–49.

It will be seen that none of the 296 patients who come under the headings of no operation, gastrostomy, or Souttar's tube survived beyond two years, and that 93% of them were dead in the first year. This is in accord with general experience and has already been stated to be the finding published by Smithers (1957).

For the purpose of the surgical follow-up the 72 patients were used who survived surgical excision before December, 1954. The use of these patients allows of a two-year follow-up which can be compared with the figures already given. In table VI the total numbers are given for operations at each level in the œsophagus and the numbers of patients who survived two years.

The 72 patients who survived surgical excision before December, 1954, have been analysed in table VI. It is to be noted that a third of all cases survived beyond the two-year stage and that the figures for the middle and lower œsophagus are closely similar. These findings correspond very closely to the figures found in other published series.

In table VII a calculation has been made of the expectation of life of a patient who has a surgical resection of a growth with the inclusion of the surgical mortality. For this calculation the survival-rates in table VI have been used and combined with the operative mortality from the last 100 cases as shown in table III.

The conclusion is that the expectation is about the same for the middle and the lower œsophageal resections, but that, when the operative mortality is included, it reduces the prospects for the upper parts more than the lower.

TABLE VII—EXPECTATION OF BEING ALIVE 2 YEARS AFTER OPERATION INCLUDING OPERATIVE MORTALITY

Site of cancer	Percentage
Mid. 1	22
Mid. 2	27
Lower	31

This is a calculation of the expectation of life with the inclusion of the operative mortality. For this the operative mortality of the last 100 cases has been combined with the follow-up findings from table VI.

Apart from actual expectation of life, it is important to assess how comfortable and enjoyable this period can be. Many people consider that the magnitude of the operation makes it undesirable for elderly patients. It seems reasonable to judge this from an inquiry into three points: the postoperative stay in hospital; the state of nutrition after operation; and any severe post-operative discomfort.

Postoperative Stay in Hospital.—A long stay in hospital might be due to major complications or to the extensive nature of the operation. Clearly either would be very undesirable in elderly people. To demonstrate the actual position the details of the last 50 discharges were reviewed. It has not been the practice in this series to hurry the patients out of hospital, and it would ordinarily have been expected that the patient would be discharged on the seventeenth to twenty-first day after operation. In 47 (94%) cases the post-operative recovery was described as uninterrupted, and for 44 of these the average time was 19 days. In 3 cases it was prolonged to thirty-nine, thirty-nine, and thirty-two days. In 2 of these it was because of

difficulties with the patient's home conditions and in one because treatment was being given to improve a cough with purulent sputum which had been present before operation. In 3 (6%) cases discharge was delayed by complications: 2 of these were because of prostatic obstruction, and in both the condition was treated surgically. Discharge was delayed for six weeks after the œsophageal operation in 1 case, and for seventeen weeks in the other. The other complication was 1 burst abdominal wound. This patient was discharged on the thirtieth day. These figures support the clinical impression that these old people tolerate this operation remarkably well.

Postoperative State of Nutrition.—All these patients took an almost normal diet. This was readily possible in all but 2 patients: one of these needed many œsophagoscopies for dilatation after an œsophago-jejunal anastomosis, and the other needed a single dilatation only. The only reason for having to qualify the statement about the diet has been a poor dental state. All the patients, including the 2 just mentioned, steadily gained weight. This satisfactory nutritional state was considered to be due to some extent to the high proportion of œsophago-gastric anastomoses, but the difference between these and the œsophago-jejunal anastomoses is not very apparent in the follow-up and cannot be brought out by figures. The only special step that is taken is to warn the patient of the difficulty that he will have in eating as much as a normal person. They are asked to concentrate on taking as much as possible and to have extra small meals at 11.00 A.M. and before they go to bed.

Severe postoperative discomfort has never been found. It is remarkable how little these patients complain of the wound discomfort which might be expected. No patient has had any symptoms of acid regurgitation. This has probably been avoided by the closure of the mediastinum at operation, and the provision of a wedge for the patient to use at night. All the patients are trained in sleeping propped against a bed-wedge while in hospital and are carefully instructed that they must use one for the rest of their lives. It is always emphasised that they must use the wedge whether they are at home or away. It is very easy, after receiving full instructions, for them to go to a convalescent home where no bed-wedge is available.

Conclusions

This review has brought no evidence for or against surgery for the upper œsophagus. It was considered at the outset that operations requiring removal of the larynx were undesirable, and only 2 are included. The small experience available confirms statements that early spread of the growth may be expected. The view expressed by Smithers (1957) and many others that these growths respond well to deep X-ray therapy has been accepted, and where necessary a Souttar's tube has been inserted before this treatment.

For the middle and lower parts of the œsophagus there seems to be a very strong case for surgical excision wherever this is possible. It is not suggested that the results are good, but it does seem worth while to have three times as many patients alive after two years as with radiotherapy. What is even more important is that these patients are well and comfortable.

Summary

The indications for the use of radiotherapy and surgery for carcinoma of the œsophagus and cardia are considered.

Personal experience of the treatment of 336 patients with this condition is described.

150 patients were treated by resection, with a mortality of 14% in the last 100 cases.

Follow-up figures for the lower and middle œsophagus are given to show that about a quarter to a third of patients submitted to resection may be expected to live more than two years.

It is emphasised that the operation is well tolerated and complications are few.

Life after resection should be comfortable and pleasant.

REFERENCES

Allison, P. R., Borrie, J. (1949) *Brit. J. Surg.* **37**, 1.
Garlock, J. H. (1947), *Ann. R. Coll. Surg. Engl.* **2**, 183.
Humphreys, G. H. jun., Moore, R. L. (1953) *Surg. Clin. N. Amer* **33**, 389.
Köhler, R. (1951) *Acta radiol., Stockh.* **35**, 207.
Krebs, C., Nielsen, H., Andersen, P. E. (1949) *Ibid*, **32**, 304.
Luppinger, A. (1936) *Eng. d. Med. Qtr.* **7**, 389.
MacManus, J. E., Paine, J. R., Dunn, J., Merdinger, W. (1956) *Surgery*, **40**, 510.
Mustard, R. A., Ibberson, O. (1956) *Ann. Surg*, **144**, 927.
Parker, E. F., Jenkins, L. B. (1955) *J. thorac. Surg.* **29**, 373.
Smithers, D. W. (1957) *Ann. R. Coll. Surg. Engl.* **20**, 36.
Sweet, R. H. (1952) *Surg. Gynec. Obstet.* **94**, 46.
— (1954) *J. Amer. med. Ass.* **155**, 422.
Torek, F. (1913) *Ibid*, **60**, 1533.
Watson, T. A., Brown, E. M. (1951) *J. thorac. Surg.* **22**, 216.
Wu, Y. K., Loucks, H. H. (1951) *Ann. Surg.* **134**, 946.

DEFICIENCY OF ANTIHÆMOPHILIC GLOBULIN IN HETEROZYGOUS HÆMOPHILIC FEMALES

A. S. DOUGLAS
M.D., B.Sc. Glasg., M.R.C.P., M.R.C.P.E., F.R.F.P.S.
LECTURER IN MEDICINE, UNIVERSITY DEPARTMENT OF MEDICINE, ROYAL INFIRMARY, GLASGOW

I. A. COOK
M.B. Aberd.
SENIOR REGISTRAR IN PATHOLOGY, SOUTHERN GENERAL HOSPITAL, GLASGOW

HÆMOPHILIA is a hæmorrhagic disease mostly affecting males and inherited as a sex-linked recessive character. In this disease the plasma is believed to be deficient in a specific clotting factor called antihæmophilic globulin.

By sex-linked recessive inheritance all the daughters of a hæmophilic man are transmitters of hæmophilia, whereas all his sons are healthy. In the family of a transmitter female the chances are that half the sons are hæmophilic and half the daughers transmitters.

The homozygous hæmophilic state in the female can theoretically result from the marriage of a hæmophilic man and a transmitter female. Such cases have been described by Treves (1886), Merskey (1951a), and Israels et al. (1951).

We report here a significant hæmorrhagic tendency due to a deficiency of antihæmophilic globulin in two heterozygous transmitter hæmophilic females.

The Patients

Two sisters, the daughters of a hæmophilic male, were studied. Their family tree is shown in fig. 1.

Case 1.—v.13 was a spinster, aged 28, who presented with protracted bleeding after tonsillectomy. She bled for six days and required the transfusion of four pints of blood.

She had always bruised easily. At the age of 9 years she fell astride a desk and bled for nine days from a vaginal wound. On each of three occasions when teeth had been extracted she had bled for five days. At the age of 22 she was admitted to hospital with an acute abdominal emergency. At laparotomy free blood was found in her peritoneum, its source being a cyst of her right ovary. Menstruation had often been heavy and prolonged, sometimes lasting nine days.

Physical examination was negative.

Case 2.—v.12 was a married woman aged 32. She also had always bruised easily. At the age of 18 she bled for a week after tonsillectomy. After tooth extraction she used to bleed for five days. At 26 her appendix was removed without causing abnormal hæmorrhage, and at 32 a forceps delivery of her first child did not cause undue hæmorrhage.

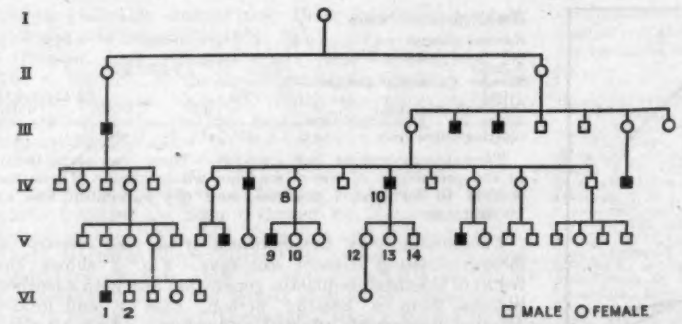


Fig. 1—Family tree of cases 1 and 2 (V.13 and V.12). Numerals refer to members of the family mentioned in the text. Solid black symbols denote hæmophilia.

The Relations

The father, IV.10, died from gastro-intestinal bleeding, but otherwise his hæmophilia was clinically mild. He had no disability of his joints and served with the infantry in the first world war. After tooth extraction and other small injuries he used to bleed for two weeks.

The mother had no hæmorrhagic tendency, and none was found in her relations.

The brother, V.14, had no hæmorrhagic tendency.

A male paternal cousin, V.9, had hæmarthrosis of his right knee at the age of 6 years and of his right elbow subsequently. He had also had recurrent muscle hæmatomata. He had one attack of hæmatemesis and used to bleed for two or three weeks after tooth extraction. His overall disability, however, was slight, and he had played rugby football.

A paternal aunt, IV.8, *and her daughter*, V.10, were said to bruise easily.

A distant male cousin, VI.1, aged 9 years, had a history of recurrent epistaxis and gum bleeding since the age of 5 years. He had once had a hæmarthrosis of his right knee.

The brother of VI.1, VI.2, died unexpectedly at the age of 6 weeks from shock two days after an uncomplicated Ramstedt operation for congenital pyloric stenosis.

Methods

Bleeding-time

Ivy's method described by O'Brien (1951).

Tourniquet Test

As described by Biggs and Macfarlane (1953).

Platelet-count

As described by Dacie (1956).

Platelet-rich Plasma

Venous blood was collected and mixed with 3·8% sodium citrate in the proportion of 9 parts of blood to 1 part of citrate in a graduated centrifuge tube.

Assessment of Blood-thromboplastin System

Theoretically, during blood coagulation thrombin is formed from a precursor—prothrombin. According to the classical theory of blood coagulation (Morawitz 1905) this conversion of prothrombin to thrombin is brought about by thromboplastin acting in the presence of calcium. The thrombin then interacts with fibrinogen to produce fibrin.

When the classical theory was put forward, it was thought that the thromboplastin was derived entirely from damaged tissue; it is now appreciated that blood withdrawn by clean venepuncture without contamination by the tissues coagulates under the influence of its own thromboplastin. This blood-thromboplastin is now known to be of great potency and is essential for physiological hæmostasis. The relative rôles of these tissue-thromboplastin and blood-thromboplastin systems, in physiological hæmostasis, is uncertain.

The constituents of this blood-thromboplastin are platelets and several plasma factors. It is accepted for the present that three plasma factors are concerned in the formation of this thromboplastin, but there may well be others. These constituents are antihæmophilic globulin (missing in hæmophilia), platelets (missing in thrombocytopenia), Christmas factor (missing in Christmas disease), and factor V (missing as a rare congenital anomaly). These components can be substituted for the thromboplastin of the classical theory.

Whole-blood Coagulation-time

This was measured by the method of Lee and White (1913) described by Biggs and Macfarlane (1953). This is a crude test of the blood-thromboplastin system and may give a normal result in the presence of a significant deficiency of thromboplastin.

Recalcification-time

0·5-ml. amounts of platelet-rich plasma are recalcified with 0·5-ml. amounts of M/40 calcium chloride in tubes $^1/_2$ in. in diameter maintained at 37°C, and the coagulation-time is recorded. This also is a test of the blood-thromboplastin system but it has the same limitation of sensitivity as the whole-blood coagulation-time.

Thrombin-generation Test

This was done on whole blood as described by Macfarlane and Biggs (1953). In this test blood is delivered to a glass tube, and by subsampling at intervals into fibrinogen the pattern of thrombin formation is studied. In the presence of a deficiency of thromboplastin the formation of thrombin may be delayed and decreased.

Prothrombin Consumption

When normal blood is collected by clean venepuncture, delivered to a glass tube, and maintained at 37°C for an hour, there is no appreciable amount of prothrombin left. When the blood-thromboplastin system is defective, the consumption of prothrombin is also defective. This test was made on whole blood by Merskey's (1951b) technique.

The ability of plasma from these patients and from controls to correct the prothrombin consumption of recalcified hæmophilic plasma was also studied.

Blood was collected from a severely affected hæmophiliac with a greatly prolonged whole-blood coagulation-time and citrated. The platelet-rich plasma from this was obtained by centrifugation. 0·5 ml. of this plasma was delivered to each of thirty-six tubes $^1/_2$ in. in diameter. To each of the first twelve tubes was added 0·05 ml. of normal plasma, to the second twelve tubes 0·05 ml. of case 1 or case 2 plasma, and to the third twelve tubes 0·05 ml. of the same hæmophilic plasma as was already in the tubes. With each set of twelve tubes are needed (1) a further twelve tubes each containing 0·2 ml. of saline solution, 0·2 ml. of brain-thromboplastin, and 0·2 ml. of M/40 calcium chloride, and (2) a further twenty-four tubes each containing 0·4 ml. of fibrinogen.

The tubes in each original set are calcified almost simultaneously with 0·125 ml. of M/10 calcium chloride. At 5-minute intervals up to 60 minutes one tube of the set is tested by removing any clot which may have formed on a wooden applicator stick and transferring 0·2 ml. into the tube containing saline solution, brain, and calcium. At this point a further stop-watch is started, and at 45 seconds and 90 seconds 0·1 ml. is transferred from this tube into the 0·4 ml. of fibrinogen, and the clotting-time is recorded. These clotting-times of fibrinogen are then expressed as thrombin units from a thrombin-fibrinogen dilution curve (Biggs 1951).

This technique was modified to give a quantitative assay of antihæmophilic globulin.

0·1 ml. of normal plasma was added to 1·0 ml. of platelet-rich hæmophilic plasma, and doubling dilutions were made in 0·5-ml. amounts of hæmophilic plasma. 0·05 ml. of either case 1 or case 2 plasma was added to a further 0·5-ml. amount of platelet-rich hæmophilic plasma. The tubes were then recalcified at 5-minute intervals and each tested at 40 minutes after recalcification as described above. The result obtained with the test specimen was then compared with the dilution curve of the normal and thereby an assay made.

A similar technique was used for assay of the Christmas factor with Christmas-disease plasma as the substrate.

Thromboplastin Generation

A platelet suspension can be prepared by differential centrifugation of citrated blood. When normal plasma is treated with an adsorbing inorganic precipitate—e.g.,

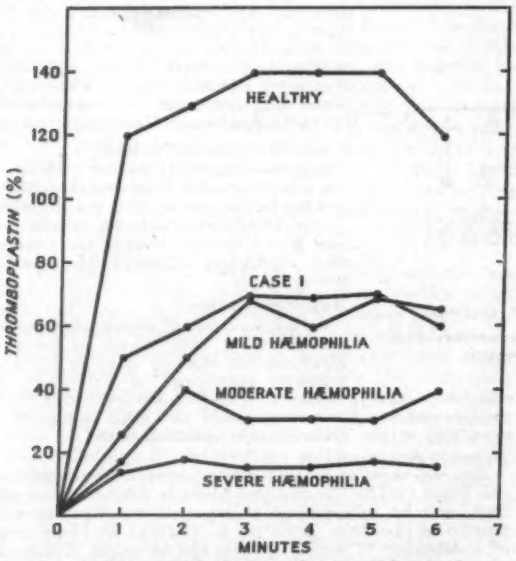


Fig. 2—Results of thromboplastin-generation test with normal serum and normal platelets constant and with adsorbed plasma variable.

aluminium hydroxide—the supernatant plasma after centrifugation contains factor V and antihæmophilic globulin. Normal serum contains the Christmas factor freed from prothrombin, antihæmophilic globulin, and factor V, which are used up during coagulation. When normal adsorbed plasma, platelets, normal serum, and calcium are incubated together, a powerful thromboplastin is formed. This is the basis of the thromboplastin-generation test (Biggs and Douglas 1953) used in the study of these two cases.

The test was modified to give an assay of antihæmophilic globulin. With reagents prepared as described in the original technique, doubling dilutions of the normal and test adsorbed plasmas were made in hæmophilic adsorbed plasma. These were then mixed with platelets and normal serum and recalcified. Each incubation mixture was tested for its thromboplastin content at six minutes after recalcification. By comparison of the test specimens with the dilution curve of the normal an assay of antihæmophilic globulin was made.

By similar principles, with normal adsorbed plasma and platelets constant, an assay was made of the Christmas factor by making mixtures with Christmas-disease serum.

One-stage "Prothrombin" Test

This was performed as described by Biggs and Macfarlane (1953) using brain-thromboplastin as prepared by Brown and Douglas (1952).

Results

The findings may be summarised as follows:

Test	*Case 1*	*Case 2*
Whole-blood coagulation-time (min.)	10, 10, 11, 11	9, 9, 10, 11
Bleeding-time (min.)	3½	4
Hess test	Negative	Negative
Platelet-count per c.mm.	335,000	310,000
Prothrombin-consumption index (Merskey)	73%	56%
Antihæmophilic globulin assay:		
By the thromboplastin-generation test (mean of 6 observations)	22%	18%
By the prothrombin-consumption technique	17%	24%
Christmas-factor assay:		
By the thromboplastin-generation test	100%	100%
By the prothrombin-consumption technique	96%	92%
One-stage prothrombin test (sec.)	17	17 (control 16)

Recalcification-times:

Normal plasma (ml.)	0·5					0·025		0·025	
Severe hæmophilic plasma (ml.)		0·5				0·475	0·475		
Severe Christmas-disease (ml.)			0·5					0·475	0·475
Case-1 plasma (ml.)				0·5			0·025		0·025
Clotting-times (min.)	3	8	10½	4½	3½	6¼	4¼	4	

Thrombin-generation test (case 1).—There was some delay in the generation of thrombin from whole blood. Thrombin started to form at 7 minutes, and the maximum was at 10 minutes.

Comparison with hæmophiliacs of varying severity on thromboplastin-generation technique.—Fig. 2 shows the result of the thromboplastin-generation test with adsorbed plasma from a healthy person, case 1, and mildly affected, moderately affected, and severely affected hæmophiliacs, with the normal serum and platelets constant.

Prothrombin consumption of recalcified hæmophilic plasma.—Fig. 3 and the accompanying table show the prothrombin consumption of recalcified hæmophilic plasma alone, and with additions of healthy and case-1 plasma. The results are the mean of three observations. One test was made on case 2 and gave similar results.

PROTHROMBIN CONSUMPTION OF RECALCIFIED HÆMOPHILIC PLASMA WITH IDENTICAL ADDITIONS OF NORMAL PLASMA, CASE-1 PLASMA, AND HÆMOPHILIC PLASMA

—	Incubation-time (min.)											
	5	10	15	20	25	30	35	40	45	50	55	60
Added plasma	Clotting-time (sec.)											
Normal	14	28	43	54	59	63	63	71	55	56	80	70
Case 1	14	17	18	16	14	15	17	17	17	14	19	15
Hæmophilic	11	12	12	14	13	14	13	11	11	12	13	11

Mother and brother V.14 of cases 1 and 2.—These were investigated by the whole-blood coagulation-time, prothrombin-consumption index, thromboplastin-generation test, platelet-count, Hess test, and bleeding-time. No abnormality was detected.

Male cousin of cases 1 and 2.—V.9 was investigated by Dr. J. V. Dacie in the department of hæmatology of the Postgraduate Medical School of London. V.9's whole-blood coagulation-time was slightly longer than normal, prothrombin consumption defective, and bleeding-time prolonged. By a modification of the thrombo-

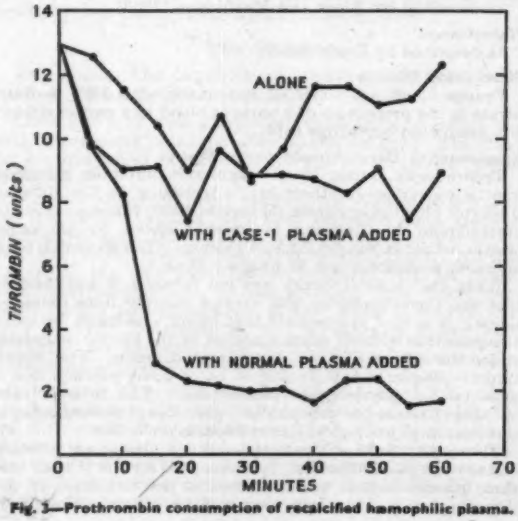


Fig. 3—Prothrombin consumption of recalcified hæmophilic plasma.

plastin-generation test (Pitney 1956) the antihæmophilic globulin was assayed at 16%.

Distant male relation.—VI. 1 was investigated by Dr. S. Lavelle, of the department of pathology of the Central Hospital, Galway. Using the thromboplastin-generation technique he found a deficiency of anti-hæmophilic globulin.

Discussion

The published reports of female "bleeders" in hæmophilic families has been reviewed by Merskey (1951a), Israëls et al. (1951), and Margolius and Ratnoff (1956). There is reasonable evidence, on clinical, genetic, and laboratory grounds, that the female patients described by Merskey (1951a) and Israëls et al. (1951) were homozygous hæmophiliacs; these cases were reported before the recognition of Christmas disease. The patient reported by Israëls et al. (1951) was subsequently retested by current methods and shown to have a pure deficiency of antihæmophilic globulin (Israëls 1957); the two sisters described in the present study were thought to be heterozygous for hæmophilia, but nevertheless to have a significant hæmorrhagic tendency.

There has been much conflicting information about the hæmostatic mechanism in female transmitters of hæmophilia. The laboratory evidence for and against change in the coagulation mechanism in these women has been carefully reviewed by Margolius and Ratnoff (1956), who also report their own findings in twenty-seven carriers. A level of antihæmophilic globulin definitely lower than normal was found in only one carrier. Merskey and Macfarlane (1951) studied the coagulation mechanism in female carriers of hæmophilia. The prothrombin-consumption test gave three positive results among twenty-one known carriers, and the readings of the group as a whole were slightly in excess of those of healthy controls. The available evidence suggests that in only very few female carriers can a significant defect be demonstrated by currently available techniques.

It was thought to be of interest that our patients belonged to a hæmophilic family in whom the affected male members had a relatively mild form of the disease.

Graham et al. (1953) reported a mildly affected hæmophilic family in which the levels of antihæmophilic globulin were low in about half of the known female transmitters of the defect. Similar assays on the mothers of severely affected hæmophiliacs gave normal results (Graham 1956).

Fantl and Margolis (1955) report the case of a heterozygous female with a demonstrable deficiency of antihæmophilic globulin and a hæmorrhagic tendency similar in degree to that present in our patients. This female was the mother, however, of a severely affected male hæmophiliac.

Quick and Hussey (1953) report the case of a girl with a coagulation defect believed to be similar to hæmophilia. There was no history of similarly affected relations.

Summary

Two sisters with a significant hæmorrhagic tendency were investigated. They proved to have a coagulation disturbance due to a deficiency of antihæmophilic globulin. This deficiency was revealed by thromboplastin-generation and prothrombin-consumption tests.

The patients were the daughters of a hæmophiliac and therefore were transmitters of the disease. The male affected members of the family had mild hæmophilia.

Our thanks are due to Prof. L. J. Davis and Dr. A. Dick for helpful advice in the preparation of this paper, and Miss Kathleen Mair for valuable technical assistance: we are indebted to Dr. J. V. Dacie, of the Postgraduate Medical School of London for the laboratory investigation of the patient V.9; and Dr. S. Lavelle of the department of pathology, Regional Hospital, Galway, for the investigation of patient V.1. One of us (A. S. D.) is grateful to the Advisory Committee on Medical Research for Scotland for a grant for equipment and to the Medical Research Council for a grant for technical assistance.

REFERENCES

Biggs, R. (1951) Prothrombin Deficiency. Oxford.
— Douglas, A. S. (1953) *J. clin. Path.* **6**, 23.
— Macfarlane, R. G. (1953) Human Blood Coagulation and its Disorders. Oxford.
Brown, A., Douglas, A. S. (1952) *Glasg. med. J.* **33**, 225.
Dacie, J. V. (1956) Practical Hæmatology. 2nd ed., London.
Fantl, P., Margolis, J. (1955) *Brit. med. J.* i, 640.
Graham, J. B. (1956) *Amer. J. hum. Gen.* **8**, 63.
— McLendon, W. W., Brinkhous, K. M. (1953) *Amer. J. med. Sci.* **225**, 46.
Israëls, M. C. G. (1957) Personal communication.
— Lempert, H., Gilbertson, E. (1951) *Lancet*, i, 1375.
Lee, R. I., White, P. D. (1913) *Amer. J. med. Sci.* **145**, 495.
Macfarlane, R. G., Biggs, R. (1953) *J. clin. Path.* **6**, 3.
Margolius, A. jun., Ratnoff, O. D. (1956) *J. clin. Invest.* **35**, 1316.
Merskey, C. (1951a) *Quart. J. Med.* **20**, 299.
— (1951b) *J. clin. Path.* **3**, 130.
— Macfarlane, R. G. (1951) *Lancet*, i, 487.
Morawitz, P. (1905) *Ergebn. Physiol.* **4**, 307.
O'Brien, J. R. (1951) *J. clin. Path.* **4**, 272.
Pitney, W. R. (1956) *Brit. J. Hæmat.* **2**, 250.
Quick, A. J., Hussey, C. V. (1953) *Amer. J. Dis. Child.* **85**, 698.
Treves, F. (1886) Cited by Merskey (1951a).

THE INCIDENCE OF PATHOGENIC ESCHERICHIA COLI IN ROUTINE FÆCAL SPECIMENS

D. R. GAMBLE M.B. Lond., Dip.Bact.
K. E. K. ROWSON M.A., M.B. Camb., Dip.Bact.
From the Central Public Health Laboratory, Colindale, London

CERTAIN serologically identifiable types of *Escherichia coli* are now generally accepted as a cause of gastro-enteritis in infants, but their relation to intestinal disease in older children and adults is less well established (Smith 1954, Herweg et al. 1956).

In nurseries and hospitals these organisms appear to spread with remarkable ease from one baby to another, and it is sometimes possible to demonstrate infection with them among members of the staff (Ochlitz and Schmidt 1955); but the incidence in the general population is unknown and difficult to determine, partly because fæcal specimens are not obtainable from an unselected sample of the population, and partly because we have no selective media to aid in the isolation of pathogenic *Esch. coli* from other lactose-fermenting organisms. The lack of a selective medium may be one reason why they are not more often isolated from nurses attending infants with gastro-enteritis.

It is the usual practice in most laboratories to examine fæcal specimens for *Esch. coli* only when the patient is aged less than 2 years, because this organism is considered of doubtful significance in older children and adults. There is therefore very little information on the presence of pathogenic *Esch. coli* in the fæcal specimens examined in any given laboratory, and it was to determine this that the present investigation was undertaken. For a year all fæcal specimens sent to the laboratory were examined for *Esch. coli* of the serological O groups that have been associated with infantile diarrhœa.

Materials and Methods

The investigation began in February, 1955, and for a year all specimens of fæces and rectal swabs received at the laboratory were plated on MacConkey's neutral-red bile-salt lactose-agar medium in addition to the routine media used in the isolation of salmonellæ and shigellæ. After overnight incubation at 37°C the MacConkey plates were examined for serologically identifiable *Esch. coli* by slide agglutination. A sweep of growth was taken from the plate, suspended in 0·9% saline solution on a microscope slide and tested for agglutination with pooled rabbit sera containing agglutinins to both O and B antigens. Usually, and always when the lactose-fermenting colonies did not appear to be of one type, individual colonies were picked and tested in the same way.

For the first eight months of the investigation two pooled sera were used. They were kindly provided by the Salmonella Reference Laboratory, Colindale, and contained OB antibodies against the following ten types of *Esch. coli* :

O 26 : B6	O 114 : B†
O 28 : B†	O 119 : B14
O 55 : B5	O 125 : B15
O 86 : B7	O 126 : B16
O 111 : B4	O 128 : B12

For the last four months three pooled sera were used : one supplied by the Standards Laboratory for Serological Reagents, Colindale, contained OB antibodies against *Esch. coli* O 26 : B6, O 55 : B5, O 111 : B4, O 119 : B14, and O 128 : B12 ; and the other two supplied by the Salmonella Reference Laboratory contained OB antibodies against the following ten sero-types :

O 20 : B†	O 124 : B17
O 28 : B†	O 125 : B15
O 40 : B†	O 126 : B16
O 86 : B7	O 127 : B8
O 114 : B†	E 1385 (3)

Any cultures showing agglutination with one of the pooled sera were subcultured on blood-agar plates ; the pure culture was tested next day with the pooled sera and individual sera. The identification was checked by tube agglutination, a boiled suspension of organisms and dilutions of the individual OB serum being used. The identification was usually confirmed by the Salmonella Reference Laboratory.

Results

During the year specimens of fæces or rectal swabs were received from 1459 patients. These patients may be divided into three groups : hospital patients both adults and children ; children in nurseries ; and patients living at home. Table I shows the age-distribution of patients in each group and the number found to be excreting *Esch. coli* of one of the types under study.

TABLE I—AGE-DISTRIBUTION OF PATIENTS AND INCIDENCE OF IDENTIFIABLE *Esch. coli* EXCRETERS

Material	Age (yr.)					
	0–1	2–4	5–14	15–64	65 or more	Total
Hospital patients :						
Examined	35	48	68	87	5	243
Positive	7 (20%)	1 (2%)	3 (4%)	2 (2%)	0	13 (5%)
Children in nurseries :						
Examined	182	81	10	..	..	273
Positive	48 (26%)	17 (21%)	2 (20%)			67 (25%)
Patients at home :						
Examined	80	107	194	513	49	943
Positive	3 (4%)	2 (2%)	3 (1·5%)	10 (2%)	0	18 (2%)
Total :						
Examined	297	236	272	600	54	1459
Positive	58 (20%)	20 (8·5%)	8 (3%)	12 (2%)	0	98 (7%)

Hospital Patients.—These were nearly all in a small isolation hospital, and many of them were admitted because of intestinal symptoms. Of the 243 patients from whom specimens were received 13 were excreting *Esch. coli* of one of the types under investigation. 11 of these patients had either diarrhœa or gastro-enteritis, but 5 of them were also excreting either a salmonella or *Shigella sonnei*. Of the remaining 6 patients with intestinal symptoms 4 were infants aged less than 2 years, 1 was aged 5 years, and 1 was an adult who had been in contact with a child excreting both *S. sonnei* and *Esch. coli* O 125 : B15. It seems probable that the *Esch. coli* isolated from the 5 young children with gastro-enteritis were responsible for the disease, but the part played by the *Esch. coli* isolated from the other patients is doubtful.

Patients in Nurseries.—During the year specimens were received from eight nurseries. In six of them (table II) excreters of pathogenic *Esch. coli* were found, but only from nurseries A and B were specimens received regularly and something approaching 100% of the children examined. Nurseries A and B were both residential, but nursery A had a very slow turnover, and the children remained for several months, whereas in nursery B there was a very much more rapidly changing population. In nursery A two sero-types of *Esch. coli* were isolated : O 111 : B4 and O 125 : B15. These two types were present when observations were begun in February ; they disappeared in March, and no typable *Esch. coli* were isolated until the following January, when the same two types were again isolated. In nursery B the predominant strain was O 119 : B14, but three other types were isolated from 1 patient each. Nurseries C and D each yielded three sero-types, but from nurseries F and H only one type was isolated. It was impossible to obtain specimens from the nurses and domestics in adequate numbers, but the few examined proved negative.

TABLE II—DISTRIBUTION OF PATIENTS IN EIGHT NURSERIES FROM WHICH SPECIMENS WERE RECEIVED

—	Nurseries							
	Residential		Day					
	A	B	C	D	E	F	G	H
No. of children examined	99	84	38	23	10	7	3	9
No. excreting typable *Esch. coli*	33 (33%)	16 (19%)	7 (18%)	7 (30%)	0	2 (29%)	0	2 (22%)

Patients at Home.—About half these patients were adults aged 15–65, and of the 513 patients in this age-group 10 were excreting *Esch. coli* of one of the types associated with infantile gastro-enteritis. The numbers of patients in the other age-groups (table I) are very much smaller, but there seems to be no substantial difference in the percentage of excreters between the age-groups. Of the 18 domiciliary patients excreting pathogenic *Esch. coli* 5 were symptom-free ; 3 others were excreting either a salmonella or *S. sonnei*. Of the remaining 10 with intestinal symptoms 5 were children aged less than 5 years, 1 was aged 12 years, and the remaining 4 were adults.

Discussion

From table I it appears that children aged less than 2 years are very much more commonly excreters of the *Esch. coli* strains under investigation than are adults, but this was only true of children in institutions where special factors operate.

Many of the hospital patients, both adults and children, were admitted because of diarrhœa, though *Esch. coli* is only rarely a cause of diarrhœa after the age of 2 years. Therefore among the hospital patients there was a strong selective factor leading to the admission of a high proportion of children excreting pathogenic *Esch. coli*.

In the nurseries the high percentage of excreters of pathogenic *Esch. coli* may be explained partly by the fact that specimens were often sent when there were cases of diarrhœa among the children and partly by the fact that many of the children were examined frequently. Table III illustrates the importance of this last factor in nursery A, which had the highest infection-rate. Payne and Cook

TABLE III—RELATION BETWEEN NUMBER OF SPECIMENS EXAMINED AND NUMBER OF EXCRETERS FOUND IN NURSERY A

No. of specimens per patient	No. of patients examined	No. of excreters detected
< 5	50	3 (6%)
5–10	24	14 (58%)
>10	25	16 (64%)

(1950) also found that there was a considerable increase in the number of excreters detected when several specimens were examined from each patient.

The children at home did not appear to be very much more commonly excreters of the specific *Esch. coli* types than were the adults. This, however, may have been due not to a low rate of infection but merely to a short period of infection.

Thomson et al. (1956), for example, observe that babies at home are often symptomless excreters of pathogenic *Esch. coli*. They examined fæcal specimens from 111 babies at fortnightly intervals and isolated pathogenic *Esch. coli* from 18% at one time or another. On only one occasion did they find two consecutive specimens positive. Infection, therefore, must have been very transitory.

Using red blood cells on to which *Esch. coli* antigens had been adsorbed (Neter et al. 1955) found hæmagglutinating antibodies in the blood of 90% of patients aged more than 12 years but in less than 13% of babies aged less than 3 months.

If these observations are generally confirmed they would support the idea that infection with pathogenic. *Esch. coli* is common and widespread.

Stevenson (1952) and McNaught and Stevenson (1953) reported diarrhœa associated with *Esch. coli* types O 111 : B4 and O 26 : B6 in old people, but in the present investigation no pathogenic *Esch. coli* were isolated from the few patients aged more than 65. That the *Esch. coli* associated with infantile gastro-enteritis can cause diarrhœa in adults has been shown by experiments on volunteers (Kirby et al. 1950, June et al. 1953), but under natural conditions they appear rarely to do so. In the present study only 5 adults with diarrhœa were excreting pathogenic *Esch. coli* with no other cause for their diarrhœa, in spite of the fact that the commonest reason for sending a fæcal specimen for bacteriological examination is some intestinal disturbance. Therefore it seems probable that the pathogenic strains of *Esch. coli* come and go as part of the normal adult intestinal flora, and that at any one time about 1% or 2% of the population are excreting them.

Summary

For a year all fæcal specimens sent to the laboratory for bacteriological investigation were examined for *Esch. coli* of the O groups associated with infantile gastro-enteritis.

Of specimens examined from 1459 patients, 98 were positive.

The patients fell into three groups: children in nurseries, patients in an isolation hospital, and patients at home.

Of the nursery children 25% were excreting pathogenic *Esch. coli*; the incidence was related to the number of specimens examined from each child.

Of the hospital patients the children aged less than 2 years were most commonly infected, 20% being positive.

The patients at home did not show any notable variation in infection-rate with age.

It is suggested that about 1% or 2% of the adult population are excreting pathogenic *Esch. coli*.

We wish to thank Dr. Joan Taylor for supplying typing sera and for advice in the preparation of this paper; and Dr. H. D. Holt and Dr. C. E. D. Taylor for help and encouragement.

REFERENCES

Herweg, J. C., Middelkamp, J. N., Thornton, H. K. (1956) *J. pediat.* **49**, 629.
June, R. C., Ferguson, W. W., Worfel, M. T. (1953) *Amer. J. Hyg.* **57**, 222.
Kirby, A. C., Hall, E. G., Coackley, W. (1950) *Lancet*, ii, 201.
McNaught, W., Stevenson, J. S. (1953) *Brit. med. J.* ii, 182.
Neter, E., Westphal, O., Lüderitz, O., Gino, R. M., Gorzynski, E. A. (1955) *Pediatrics*, **16**, 801.
Ochlitz, H. W., Schmidt, E. F. (1955) *Helv. Pædiat. Acta*, **10**, 450.
Payne, A. M. M., Cook, G. T. (1950) *Brit. med. J.* ii, 192.
Smith, J. (1954) The Ætiology of Epidemic Infantile Gastro-enteritis. Royal College of Physicians of Edinburgh Publications, 1955, no. 5.
Stevenson, J. S. (1952) *Brit. med. J.* ii, 123.
Thomson, S., Watkins, A. G., Gray, O. P. (1956) *Arch. Dis. Childh.* **31**, 340.

PLASMA-INSULIN ESTIMATION BY THE RAT-DIAPHRAGM METHOD

PETER H. WRIGHT
M.B., M.Sc. Lpool
LECTURER IN CHEMICAL PATHOLOGY, GUY'S HOSPITAL MEDICAL SCHOOL, LONDON

Gemmill (1940, 1941) was the first to show that insulin stimulates the consumption of glucose by the isolated rat diaphragm. Since then several groups of workers have adapted the technique to the estimation of plasma-insulin in man (Groen et al. 1952, Vallance-Owen and Hurlock 1954, Randle 1954a). Details of their methods vary, and the results they have obtained are conflicting. In an attempt to confirm the results described by Vallance-Owen et al. (1954, 1955) I have repeated some of this work using a standardised method of assay.

Methods

Rats

Two strains of young male Wistar rats were used; strain-A rats were provided by the Chester Beatty Research Institute, and strain-B rats were bred on Guy's Hospital Ouborough Estate. After being fed ad lib. on a standard rat-cake diet they were starved for 24 hours, weighed, and then killed by decapitation. In each experiment eight rats were used, and their weights usually did not vary by more than 10 g. In the whole series of experiments rats weighing 100–135 g. were used.

Buffered Media

For preliminary soaking of the diaphragm, Krebs-Ringer bicarbonate buffer (K.R.B.) was used; this was made up from stock solutions at approximately weekly intervals (Umbreit et al. 1945). For incubation purposes glucose ('Analar,' Hopkin & Williams) was dissolved in K.R.B. in a final concentration of 300 mg. per 100 ml. (G.K.R.B.).

Insulin

Five times recrystallised insulin (Boots batch no. CT 4245LL, 22·2 units per mg.) was dissolved in very dilute acetic acid (6 ml. of glacial acetic acid per litre) in a final concentration of 50 units per ml. This stock solution was kept at 0°C and used for experiments up to 3 weeks later; no loss of activity was noted in this time. For each experiment the stock insulin solution was diluted serially in G.K.R.B. to final concentrations of 1000, 100, and 10 micro-units per ml.; these solutions were used immediately.

Plasma

Venous blood was drawn into a heparinised syringe, and the plasma was separated as rapidly as possible—usually within an hour. The plasma-glucose level was estimated and then raised to 300 mg. per 100 ml. by the addition of solid glucose. Such plasma was either used immediately or stored at −15°C for 1–5 days; no appreciable loss of insulin activity was noticed under these latter conditions.

Apparatus

All glass apparatus coming in contact with any solutions in which the diaphragms were suspended was thoroughly cleaned with chromic acid and distilled water; no detergent was used.

Estimation of Insulin Activity

Immediately after decapitation the rat was pinned out, and its diaphragm was removed carefully (Stadie and Zapp 1947). The diaphragm was soaked for 15 min. in cold K.R.B. (0–7°C) during which time the two hemidiaphragms were dissected out; crushing and tearing of muscle-tissue was avoided as far as possible.

The hemidiaphragms were then carefully blotted and placed in separate Warburg bottles containing 2 ml. of undiluted plasma or 2 ml. of G.K.R.B. with or without added insulin.

TABLE I—INSULIN EFFECTS OF G.K.R.B. SOLUTIONS CONTAINING KNOWN CONCENTRATIONS OF INSULIN (MEAN VALUES)

Insulin concentration (micro-units per ml.)	No. of experiments	Insulin effect (μg. of glucose per 10 mg. dry wt. per 90 min.)	S.E.
10	9	32	11·4
100	10	98	11·4
1000	17	236	8·8

Insulin effect in any one experiment = mean glucose uptake of hemidiaphragms placed in G.K.R.B. containing insulin minus mean uptake of hemidiaphragms placed in G.K.R.B. alone.

TABLE II—GLUCOSE UPTAKE OF HEMIDIAPHRAGMS INCUBATED IN G.K.R.B. CONTAINING INSULIN IN VARIOUS CONCENTRATIONS

	Insulin concentration (micro-units per ml.)			
	0 (Basal uptake)	10	100	1000
Rat strain A :				
No. of hemidiaphragms used	17	34	21	38
Glucose uptake (µg. of glucose per 10 mg. dry wt. per 90 min.)	290	314	398	516
Standard error	±9·6	±7·2	±13·0	±9·8
Rat strain B :				
No. of hemidiaphragms used	23	11	11	29
Glucose uptake (µg. of glucose per 10 mg. dry wt. per 90 min.)	334	386	460	562
Standard error	±9·6	±11·6	±14·2	±6·4

Mean values from 21 experiments using two strains of Wistar rats.

The bottles were gassed for 5 min. with a mixture of carbon dioxide (5%) and oxygen (95%) and then incubated at 37°C for 90 min. with constant shaking (120 oscillations per min. ; 4 cm. amplitude). At the end of the incubation period duplicate samples (0·2 ml.) of the incubation medium in each Warburg bottle were taken for glucose estimation ; similar samples were taken from the plasma and G.K.R.B. before incubation in the Warburg bottles. The hemidiaphragms were washed, dried for 2 hours at 110°C, and weighed ; dry weights varied between 17 and 28 mg. throughout the series of experiments.

Glucose in blood, plasma, and G.K.R.B. was estimated by a slight modification of the method described by King (1951) : after the addition of 10% sodium tungstate 3 ml. of supernatant fluid was used instead of 2 ml., and the mixture, after addition of the alkaline copper reagent, was boiled for 20 min. instead of 10.

The consumption of glucose by the rat hemidiaphragm is expressed as µg. glucose consumed per 10 mg. dry weight of tissue per 90 min. Throughout the subsequent account the amount of glucose consumed by the rat hemidiaphragm is called the " glucose uptake."

Results

Glucose Uptake in G.K.R.B. Containing Insulin

In 21 experiments the glucose uptake of hemidiaphragms placed in G.K.R.B. containing insulin was always greater than that of hemidiaphragms placed in G.K.R.B. containing none. In addition there was always a graded increase in uptake as the insulin concentration was raised from 0 to 1000 micro-units per ml. In any single experiment the uptake of hemidiaphragms placed in the same incubation medium varied by 3% at most, but occasionally there were greater individual variations ; in these latter cases a single rat was usually responsible in that both its hemidiaphragms behaved abnormally. Considerable day-to-day variations were observed in glucose uptake by hemidiaphragms placed in G.K.R.B. alone (basal uptake) ; the coefficient of variation for both series of rats was 14%. The insulin effects (i.e., the difference between uptake in the presence of added insulin and the basal uptake) in individual experiments where a direct comparison was made are shown in table I.

The mean glucose uptakes of hemidiaphragms of the two strains of rats incubated in G.K.R.B. containing various levels of added insulin are shown in table II ; in 12 experiments rats of strain A were used, strain B being used in 9. Vallance-Owen et al. (1954) have shown that there is a linear relationship between glucose uptake and the cube-root of the insulin level. The present results (fig. 1) also suggest that such a relationship does exist. The mean slopes of the lines obtained with both series of rats are the same (23·7 µg. of glucose per cube-root of insulin level in micro-units per ml.) and almost identical with that of the line (23·1 µg. of glucose per cube-root of insulin level) calculated from the figures given by Vallance-Owen et al. (1955).

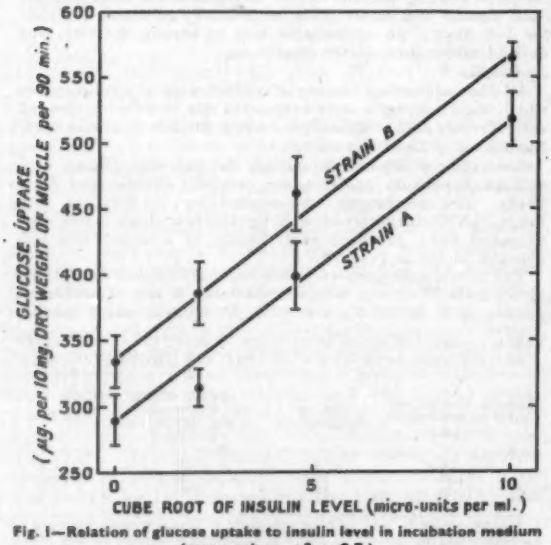


Fig. 1—Relation of glucose uptake to insulin level in incubation medium (mean values ±2 × S.E.).

Glucose Uptake in Plasma

During the experiments described above samples of plasma were also used as incubating media. Blood was drawn after 10–12 hours' fast overnight (fasting specimen) with the person at rest, and in some cases a further specimen was taken an hour after an oral dose of 50 g. of glucose (fed specimen). Uptakes of glucose by diaphragms in fasting and fed specimens of plasma from the same person were compared directly in the same experiment.

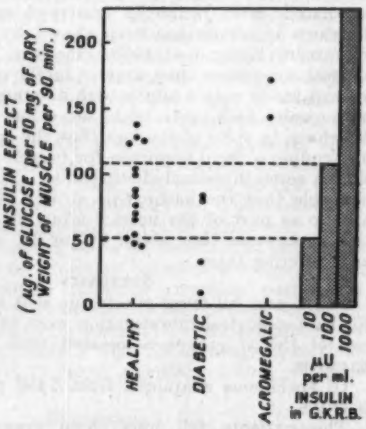


Fig. 2—Insulin effects (plasma uptake minus basal uptake) of plasma from fasting healthy people, diabetics, and acromegalics and of standard solutions of insulin in G.K.R.B.

Normal subjects.—Fasting specimens were collected from 15 people (10 males, 5 females) who were either members of the staff or hospital patients. None showed any sign of diabetes or any other endocrine disorder. They varied in age between 18 and 65. Fed specimens were obtained from 3 of these.

In 11 experiments where a direct comparison was made the uptake of hemidiaphragms in plasma (plasma uptake) was significantly greater than the basal uptake ($p<0·001$) ; the mean difference (plasma-insulin effect) was 82 µg. per 10 mg. of dry tissue per 90 min. (S.E. = ±10·2). The plasma uptake was also significantly less than that of hemidiaphragms placed in G.K.R.B. containing 1000 micro-units of insulin per ml. ; in 15 experiments the

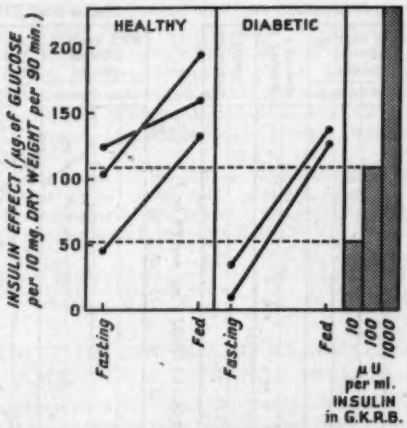


Fig. 3—Plasma-insulin effects of healthy people and of diabetics before and an hour after an oral dose of glucose 50 g.

mean difference was 154 µg. per 10 mg. dry weight of tissue per 90 min. (S.E. = ±9·8). The results of individual experiments are shown in fig. 2, which shows that most of the fasting specimens had insulin effects which were less than that of G.K.R.B. containing 100 micro-units of insulin per ml. If the mean insulin effect of these fasting specimens is interpreted in terms of insulin level by the relationship shown in fig. 1, one can conclude that normal fasting subjects have a mean plasma-insulin level of 55 micro-units per ml.

In the 3 cases where fed specimens were directly compared with fasting specimens from the same person, the insulin effect was much greater in the former (fig. 3). The plasma uptake in all 3 fed specimens was comparable to that of G.K.R.B. containing more than 100 micro-units per ml.

Diabetes mellitus.—Plasma from 4 diabetic subjects was examined. Their ages ranged between 57 and 65, 2 being obese females and 2 non-obese males. All were hyperglycæmic in the fasting state, none had ketonuria, and none was receiving insulin. Such diabetics, in contrast to young diabetics who require insulin therapy to survive, should show demonstrable plasma-insulin activity as reported by Vallance-Owen et al. (1955) and by Bornstein and Lawrence (1951).

The fasting specimens from these 4 diabetics had plasma-insulin effects comparable to those of fasting normal subjects (fig. 2). When the 2 obese females were given glucose, their fed specimens had greater insulin effects than their fasting specimens (fig. 3).

Acromegaly.—Plasma from 2 fasting acromegalics with typical physical signs but no demonstrable evidence of diabetes showed high insulin effects equivalent to a G.K.R.B. solution containing more than 100 micro-units per ml.

Discussion

The method of assay described above is very similar to that originally described by Vallance-Owen and Hurlock (1954). They showed that the effective insulin level in the plasma of normal fasting subjects was about 40–80 micro-units per ml. The present results agree well with this finding, and with a recent estimate of 65 micro-units per ml. calculated from the data of Berson et al. (1956) on the basis of experiments in which they studied the fate of labelled insulin injected into man. Somewhat higher results were obtained by two other groups of workers:

Bornstein (1950), using alloxan-diabetic hypophysectomised adrenalectomised rats, found a normal fasting plasma-insulin level of about 100 micro-units per ml. rising to 240 micro-units per ml. in plasma drawn 2½ hours after a dose of oral glucose.

Groen et al. (1952) suggested that normal plasma contains 60–600 micro-units per ml.; they used the rat-diaphragm assay method employing plasma diluted before incubation. They do not specify the conditions under which the blood was collected.

Randle (1954a), on the other hand, using the rat-diaphragm technique, found that, 2½ hours after the administration of glucose, the mean effective insulin level was about 13 milli-units per ml. This is more than twenty times the level found in the present experiments or in those of Vallance-Owen and Hurlock (1954), using plasma drawn an hour after the administration of glucose. It is impossible at present to give any definite reason for this discrepancy, but it is interesting to note that, whereas Vallance-Owen et al. (1954, 1955) and I used undiluted plasma for assay, Randle (1954a) used plasma diluted 1 : 4 and 1 : 16 for his 4-point assay method. In a few preliminary experiments I have found that plasma diluted 4 times has almost the same insulin effect as undiluted plasma. Further dilution, as shown by Randle (1954a), then causes a fall in insulin effect which is related to the degree of dilution. This could mean that, in the initial stages of plasma dilution, insulin is released from some bound or inactive form in which it is present in whole blood, or that some insulin antagonist is inactivated. Further dilution would then only dilute the insulin, which would exert a proportionate effect on the rat diaphragm. Insulin assay using undiluted plasma, therefore, would give a measure of the effective free insulin in plasma; whereas, if diluted plasma is used, the value found is more likely to approximate to the total plasma-insulin level. For the reasons put forward by Vallance-Owen et al. (1955) and by Randle (1954a) it seems likely that the effective level of insulin in plasma is measured by the rat-diaphragm technique. The effects of dilution of plasma would then indicate the degree to which insulin is antagonised or inactivated in whole plasma.

This latter point is of interest in view of the results obtained with the plasma of fasting acromegalics. The present results suggest that the plasma-insulin level in such patients is of the order of 100–1000 micro units per ml. Randle (1954b), on the other hand, using diluted plasma, got fasting levels of about 50–500 milli-units per ml.—i.e., between 100 and 1000 times the values obtained with undiluted plasma. This suggests that acromegalic plasma has a high total-insulin level and correspondingly large concentrations of insulin antagonists or inactivators. Patients with hypopituitarism, on the other hand, show plasma-insulin activities which are very low even when diluted plasma is used (Randle 1954c).

The remaining results merely confirm other findings of Vallance-Owen et al. (1954, 1955). Thus, the administration of glucose to normal fasting subjects raises their plasma-insulin activity, and diabetics who do not require insulin for survival have normal fasting plasma-insulin levels, which also rise after oral glucose.

This assay method is subject to the disadvantages of any biological technique. Nevertheless, provided a rigidly standardised procedure is adopted, it will give results which are reproducible and shed some light upon the effects of endocrine abnormalities in carbohydrate metabolism.

Summary

The plasma-insulin activity of 15 normal fasting subjects has been estimated by the rat-diaphragm method.

Results confirm previous suggestions that the effective insulin level is about 50 micro-units per ml. and is unlikely to be higher than 100 micro-units per ml.

Non-ketotic diabetics who do not require insulin therapy have similar fasting levels, whereas non-diabetic acromegalics have a fasting level about ten times as high as the normal. Administration of glucose to fasting subjects raises their plasma-insulin level in one hour.

It is suggested that the dilution of plasma before assay releases insulin by inactivating insulin antagonists or by releasing bound insulin, thereby giving rise to apparently high results.

I would like to thank Prof. A. Haddow, of the Chester Beatty Research Institute, who kindly supplied me with some of the rats; and Messrs. Boots Pure Drug Co. Ltd., Nottingham, for generous supplies of insulin. I would also like to thank various physicians of Guy's Hospital who gave me access to their patients; Prof. R. H. S. Thompson for his continued encouragement and advice, and Mr. Brian Gibson for his skilled technical assistance.

REFERENCES

Berson, S. A., Yalow, R. S., Bauman, A., Rothschild, M. A., Newerly, K. (1956) *J. clin. Invest.* **35**, 170.
Bornstein, J. (1950) *Aust. J. exp. Biol. med. Sci.* **28**, 93.
— Lawrence, R. D. (1951) *Brit. med. J.* i, 732.
Gemmill, C. L. (1940) *Bull. Johns Hopk. Hosp.* **66**, 232.
— (1941) *Ibid*, **68**, 329.
Groen, J., Kamminga, C. E., Willebrands, A. F., Blickman, J. R. (1952) *J. clin. Invest.* **31**, 97.
King, E. J. (1951) Micro-Analysis in Medical Biochemistry. 2nd ed., London; p. 20.
Randle, P. J. (1954a) *Brit. med. J.* i, 1237.
— (1954b) *Lancet*, i, 441.
— (1954c) *Ibid*, p. 809.
Stadie, W. C., Zapp, J. A. jun. (1947) *J. biol. Chem.* **170**, 55.
Umbreit, W. W., Burris, R. H., Stauffer, J. F. (1945) Manometric Techniques and Related Methods for the Study of Tissue Metabolism. Minneapolis; p. 194.
Vallance-Owen, J., Hurlock, B. (1954) *Lancet*, i, 68.
— — Please, N. W. (1954) *Ibid*, p. 983.
— — — (1955) *Ibid*, ii, 583.

Preliminary Communications

EFFECT OF CORTICOTROPHIN ON URINARY EXCRETION OF PREGNANEDIOL AND PREGNANETRIOL

THE urinary excretion of pregnanediol (pregnane-3α : 20α-diol) was increased by the administration of corticotrophin in 10 patients with healthy adrenal glands to a maximum of 7·24 mg. per twenty-four hours.[1]

The urinary excretion of pregnanetriol (pregnane-3α : 17α : 20α-triol), after the administration of corticotrophin, reached a maximum of 4·6 mg. per twenty-four hours in 4 patients with healthy adrenal glands, reached a maximum of 8·2 mg. per twenty-four hours in 5 hirsute women, and increased from 2·8 mg. per twenty-four hours to 2·7 mg. in eight hours in 1 patient with Cushing's syndrome.[2]

We have studied the effect of corticotrophin gel on the urinary excretion of pregnanediol and pregnanetriol in 23 people with healthy adrenal glands, 22 hirsute women, and 5 patients with Cushing's syndrome due to adrenal cortical hyperplasia.

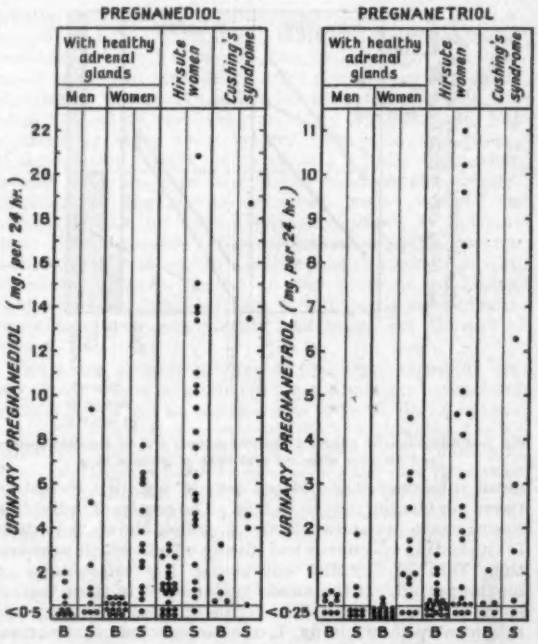
Method

Injections of 100 units of corticotrophin gel were given on three consecutive days. Urinary pregnanediol and pregnanetriol were estimated by the method of Bongiovanni and Clayton.[3] Whenever a high excretion of pregnanediol was found, part of the appropriate fraction was treated with Girard T reagent, and its ketonic and non-ketonic components were estimated. In 13 cases the pregnanediol excretion was also estimated by the method of Klopper et al.,[4] and in 12 of them the results were comparable. Urinary total 17-hydroxycorticosteroids and 17-ketosteroids were also measured, and the completeness of the urine collections was checked by creatinine determinations.

Results

The results are shown in the accompanying figure.

In most of the patients with healthy adrenal glands the administration of corticotrophin increased the urinary excretion of pregnanediol, as reported by Klopper et al.[1]



Urinary excretion of pregnanediol and pregnanetriol before (B) and on the third day of (S) stimulation with corticotrophin gel.

The effect on the urinary excretion of pregnanetriol was less consistent, and in some of the men no increase was found. Of the hirsute women 9 gave responses larger than those of the healthy people: in 3 of these pregnanediol and pregnanetriol were both affected; in 5 pregnanediol alone was affected; and in 1 pregnanetriol alone was affected. In these 9 women there was also an unusually big increase of urinary total 17-hydroxycorticosteroids and 17-ketosteroids in response to corticotrophin. In all 9 the resting levels of total 17-hydroxycorticosteroids were within the normal range, and the resting 17-ketosteroid excretion was normal in 6 of them. The highest level of pregnanetriol excretion—15·4 mg. per twenty-four hours—was found in an obese non-hirsute diabetic woman on the third day of corticotrophin (not shown in the figure).

The possibility of an extra-adrenal source of the pregnanediol and pregnanetriol was considered. 4 oöphorectomised women included in the present investigation all gave a normal response to corticotrophin. In 2 adrenalectomised women with intact functioning ovaries corticotrophin had no effect on the urinary excretion of either pregnanetriol or pregnanediol. A similar result was obtained with an adrenalectomised man with healthy testes. A pregnant addisonian and a woman who had undergone total adrenalectomy and subsequently became pregnant excreted the expected amounts of pregnanediol and traces of "pregnanetriol"; there was considerable day-to-day variation of pregnanediol excretion, but it did not appear to be influenced by corticotrophin.

Conclusions

These results give further support to the suggestion of Klopper et al.[1] that pregnanediol derived from adrenal cortical progesterone may appear in the urine and indicate the rate of steroidogenesis. Pregnanetriol is presumably derived from 17-hydroxyprogesterone, the next stage in the synthesis of hydrocortisone. The peak

1. Klopper, A., Strong, J. A., Cook, L. R. *J. Endocrin.* 1957, **15**, 180.
2. Prunty, F. T. G. *Brit. med. J.* 1956, ii, 615, 673.
3. Bongiovanni, A. M., Clayton, G. W. *Bull. Johns Hopk. Hosp.* 1954, **94**, 180.
4. Klopper, A., Michie, E. A., Brown, J. B. *J. Endocrin.* 1955, **12**, 209.

excretions of pregnanediol and pregnanetriol were often reached before that of the total 17-hydroxycorticosteroids. The high levels found in some of the hirsute women were always accompanied by high values for hydrocortisone metabolites and therefore do not indicate the presence of a significant metabolic defect comparable to that found in congenital adrenal pseudohermaphroditism.

We wish to thank the consultants of the Middlesex Hospital who allowed us to study their patients, and the clinical research committee of the hospital for providing laboratory facilities and a research grant to J. D. N. N.

J. D. N. NABARRO
M.D. Lond., F.R.C.P.
A. MOXHAM

Institute of Clinical Research, Middlesex Hospital Medical School, London, W.1

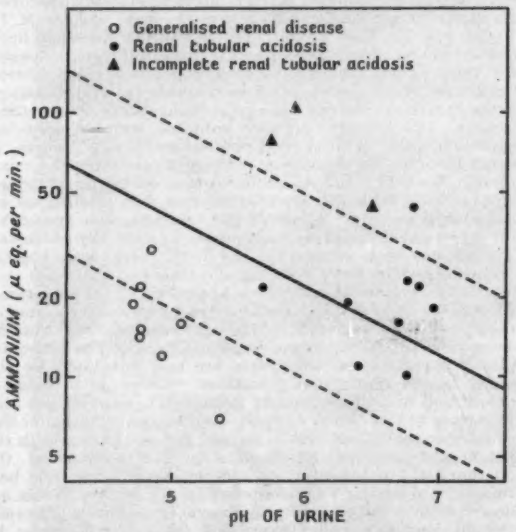
ACIDITY OF URINE AND EXCRETION OF AMMONIUM IN RENAL DISEASE

IN normal circumstances the metabolism of the body produces an excess of non-volatile acid over base, and a systemic acidosis would result were it not for the ability of the kidney to excrete a urine more acid than the body-fluids together with appreciable amounts of ammonium. The acidosis of renal disease is usually considered to be due to impairment of both these functions. We have studied the renal response to a small dose of ammonium chloride in healthy people and in patients with two types of renal disease: (1) chronic glomerulonephritis, pyelonephritis, and malignant hypertension affecting both glomeruli and tubules; and (2) renal tubular acidosis and nephrocalcinosis affecting the tubules predominantly. Each person ingested a single dose of ammonium chloride, 0·1 g. per kg. of body-weight, and urine was collected under oil at intervals during the following eight hours. The accompanying table shows the changes in the urine.

In the healthy people the pH of the urine decreased within three hours to less than 5·3 while the rate of excretion of ammonium increased. A close relationship between the rate of excretion of ammonium and the urine pH has already been shown [1]; the relationship in our healthy people was almost identical (see figure), the excretion of ammonium increasing exponentially with the decreasing pH of the urine.

URINE FINDINGS 2–8 HOURS AFTER INGESTION OF AMMONIUM CHLORIDE

—	Number of people	pH	Excretion of ammonium (μ.eq. per min.)	Clearance of endogenous creatinine (ml. per min.)
Healthy people	10	4·6–5·3	33–75	81–149
Generalised renal disease	8	4·7–5·4	7–30	7–62
Renal tubular acidosis	9	5·7–7·0	10–23	21–60
Nephrocalcinosis without acidification defect	5	4·8–5·5	46–90	44–82
Nephrocalcinosis with incomplete form of renal tubular acidosis	3	5·7–6·5	44–103	53–98



Relationship between rate of excretion of ammonium and pH of urine.

Regression line ($y = 2·89 - 0·259\ x$, where y = log. NH_4 μ eq. per min., and x = pH) was calculated from 185 observations on ten healthy people before and after taking either ammonium chloride or sodium bicarbonate; their 95% range is shown. Each point shown represents the urine of one patient after taking ammonium chloride.

In the patients with renal disease this relationship did not hold. In generalised renal disease the pH of the urine decreased normally, but the excretion of ammonium, as has long been known,[2] remained scanty. In renal tubular acidosis, on the other hand, the pH of the urine did not decrease normally; the rate of excretion of ammonium was usually low but was normal in relationship to the pH of the urine.

Of eight patients with nephrocalcinosis but without systemic acidosis five showed a normal response to ammonium chloride. The remaining three could not acidify their urine normally, but their excretion of ammonium was normal or greater than normal, and certainly high for the pH of their urine. We consider that these three patients have an incomplete form of renal tubular acidosis, but that they have so far been prevented from developing an acidosis by their high excretion of ammonium.

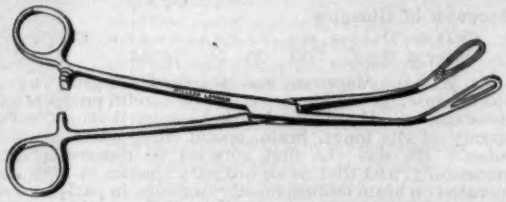
Medical Unit, Cardiff Royal Infirmary
H. E. F. DAVIES
M.D. Lond., B.Sc. Wales, M.R.C.P.

Department of Medicine, University of Manchester
OLIVER WRONG
B.M. Oxfd, M.R.C.P.

New Inventions

VEIN-HOLDING FORCEPS

OPERATIONS for varicose and recurrent varicose veins are becoming more common. Those who have done a number of them know how singularly fragile the veins are, and how a torrential hæmorrhage ensues instantly on tearing one, especially at the sapheno-femoral or the sapheno-popliteal junctions. The veins can be controlled



by the pressure of a finger or of gentle forceps that will not "chaw" the vein and make the defect worse, as hæmostats are likely to do. The forceps illustrated are a sponge forceps in miniature; they will hold a vein and other fragile tissues without crushing or injury. They have been used for over six months and have become a part of the foundation instruments for vein operations.

I have to thank Mr. V. J. Millard, 12, Springcroft Avenue, London, N.2, for his painstaking coöperation in working out their construction.

HAROLD DODD
CH.M. Lpool, F.R.C.S.
London

1. Clarke, E., Evans, B. M., Macintyre, I., Milne, M. D. *Clin. Sci.* 1955, **14**, 421.
2. Palmer, W. W., Henderson, L. J. *Arch. intern. Med.* 1915, **16**, 109.

Reviews of Books

Hemorrhagic Diseases

ARMAND J. QUICK, PH.D., M.D., professor of biochemistry, Marquette University School of Medicine. London: Henry Kimpton. 1957. Pp. 451. 70s.

ALTHOUGH Professor Quick wrote a book with this title in 1942, this volume is not a second edition but a new book. And it is by no means a conventional textbook, since the author is mainly concerned to present his own ideas on the various hæmorrhagic diseases and their underlying functional pathology. He does, however, give proper notice to the views of others; and excellent historical introductions and effective bibliographies are features of every chapter. The book thus has an individual viewpoint that is of great interest to hæmatologists familiar with the subject, because Quick's wide experience enables him to record many points about clinical findings and laboratory techniques that are not to be found elsewhere. But this individuality does mean that the book is unsuitable as the only reading for a student new to the subject.

The book is divided into a big "clinical" part and a smaller part dealing with laboratory techniques, which gives details of 25 tests that Quick considers should be available to all who have to sort out clinical hæmorrhagic syndromes; it includes some tests (e.g., one concerned with the activation of prothrombinogen) that are not in general use. The clinical chapters include one on venous thrombosis, a subject to which Quick has made important contributions.

There is evidence here and there that the book has been in preparation a long time and some of the views expressed have already been modified. Nevertheless it is essential reading for all hæmatologists, because, even if they differ with some of the ideas, the amount of practical and sensible information it contains is remarkable.

Selected Contributions to Psycho-Analysis

JOHN RICKMAN, M.D. Edited by W. CLIFFORD M. SCOTT, M.D. London: Hogarth Press and Institute of Psycho-Analysis. 1957. Pp. 411. 30s.

THIS volume contains selections from the late Dr. Rickman's published papers on psycho-analysis, together with a hitherto unpublished paper and a list of the author's publications. The 23 papers illustrate the range of Dr. Rickman's interest not only in psycho-analysis but also in art and in the technique of communications between human beings. All who are interested in the development of psycho-analysis and its relation with other cultural fields will be glad to have in permanent form such a representative selection of the writings of one of the foremost pioneers of the British school of psycho-analysis.

Macewen of Glasgow

CHARLES DUGUID, M.B., F.R.F.P.S., F.R.A.C.S. Edinburgh: Oliver & Boyd. 1957. Pp. 51. 7s. 6d.

Sir William Macewen was a general surgeon in the widest sense, basing his operations on careful preoperative investigation. He made remarkable contributions to the surgery of the lungs, brain, spinal cord, inner ear, and bones. He was the first surgeon to remove a lung successfully, and that in an ordinary theatre in 1895; he operated on brain lesions, mostly tumours, in patients sent to him from all over the world; he was largely responsible for the operation of radical mastoidectomy; and his bone work was equally successful and no less revolutionary. What is more, he was a great teacher. Macewen's talents and achievements are well recognised, but the man himself seems little known.

"Thorough" describes everything he ever did. Once when he was asked why he did not write a manual on surgery he replied "Well, you see, I am not a good collaborator. I should have to write the book myself and before it was finished the first part would be out of date." There was nothing static about Macewen's surgery. He has been criticised because he failed to found a school of surgery, but, as Mr Duguid shows, conditions at the Western Infirmary, Glasgow, over which he had no control, prevented this; but he trained a host of surgeons. He was scrupulously honest, giving credit where credit was due. Once when he operated on an unusual case of osteomyelitis of the femur he had disagreed with his assistant over the precise site of the disease. When this boy was subsequently shown to a group of visiting surgeons one of them remarked "This is a rare case, did you diagnose the upper end at once?" "No," said Macewen, stepping aside, "my house-surgeon did."

Macewen's skill and personality are vividly revealed in this short reminiscent biography.

Divorce in England

O. R. MCGREGOR. London: Heinemann. 1957. Pp. 220. 18s.

THE author says that his book is "a polemic against prejudice and ignorance . . . the comment of a historically minded social scientist" upon the history and present condition of our divorce law, and, in particular, on the report of the Morton Commission. Divorce is of medical interest both in its causes and in its effects. The invocation of social science should not lead us to expect factual information about these, for, as Mr. McGregor says, nobody has so far troubled to obtain such information before expressing an opinion on the legal and moral issues. What he gives us is a pamphlet, in the tradition of the great pamphlets, written in a style which may win the cheers even of the ranks of Tuscany who may be stung by Mr. McGregor's extremely mordant wit. But he also provides the statistical background to assertions about the disintegration of the family made by "moralists who diagnose a diseased present because they worship a past they do not understand," and he writes a remarkably readable history of the law and social standing of divorce.

Since this is still a matter of personal conviction rather than of compelling sociological evidence, doctors will be as divided as other sections of opinion, and it is probably those readers whom Mr. McGregor makes most angry who should be urged to read him: others will welcome his book as a blow for social liberalism, struck with unusual good nature and panache.

Martius' Gyneco'ogical Operations (London: J. & A. Churchill. 1957. Pp. 405. £7 5s.).—British gynæcologists have always admired the clear diagrams and masterly exposition of this operative gynæcological textbook. In this latest edition, which is really an American translation of the 7th German edition, Professor Martius has expanded and improved his illustrations. The English text is the work of Prof. M. L. McCall and Dr. Karl Bolten, of New Orleans, and they have translated and edited the German text carefully and preserved the spirit of the original. Continental practice is different from that which is acceptable in this country and, possibly, in the Americas. Martius has a great liking for the Pfannenstiel incision and stoutly defends subtotal hysterectomy—an operation which is considered obsolescent, if not obsolete, in Great Britain. He describes a number of operations for retroversion, including the Alexander-Adams in detail for which he apologises with the explanation that it is retained as an anatomical exercise. Some of the ventrofixation operations for retroversion would be unpalatable to most British tastes. The second large section of the book deals with vaginal operations which are beautifully illustrated so that each step can be followed at a glance. Here again some of the operations, such as the interposition operation and high vesicofixation of the uterus done vaginally by Halban's method, would not be acceptable to British gynæcologists. Some of the elaborate plastic operations on the cervix are now out-dated by the more simple diathermy conisation. There is a detailed description and illustration of Schauta's operation, but this will never be considered adequate as a cancer operation in this country or the United States, because it does not deal with the potentially involved lymph-glands. The account of the anatomy of stress incontinence is outstanding and the best thing in the book. Various operations for urinary fistula are described in detail and the principles here cannot be criticised, though Martius's bulbo-cavernosus fat flap will never be popular in Britain. Martius ends his book with a description of inguinal and femoral herniorrhaphy and a short chapter on intestinal surgery. If the small bowel has to be resected and anastomosed, the illustration should show it being done end-to-end and not side-to-side. This beautiful book is an effective statement of the German gynæcologist's point of view, but its price will limit its British readers.

MA3964

....but for those who find sleep difficult

'SONERYL'
trade mark brand
BUTOBARBITONE

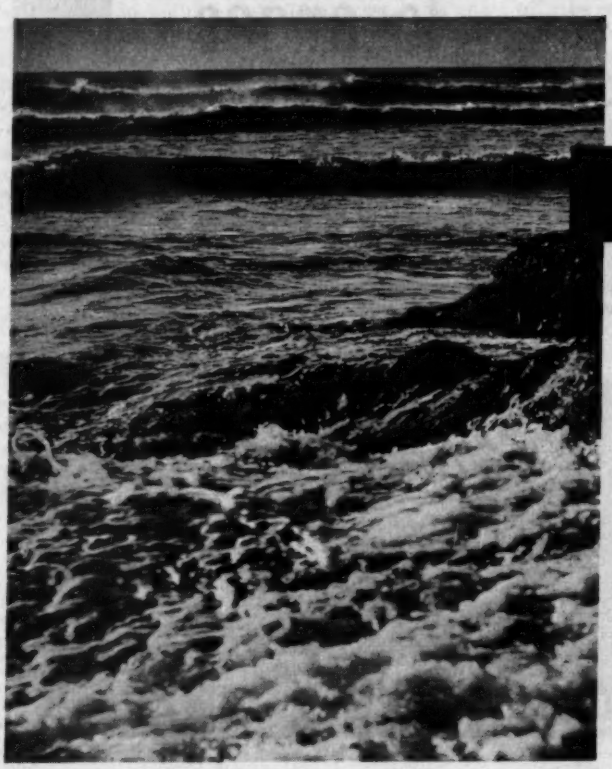
and for insomnia due to pain

'SONALGIN'
trade mark brand
BUTOPHEN WITH CODEINE

MANUFACTURED BY
MAY & BAKER LTD

M&B brand Medical Products

DISTRIBUTORS: PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD · DAGENHAM · ESSEX



Sure as the tide will turn

you can be sure

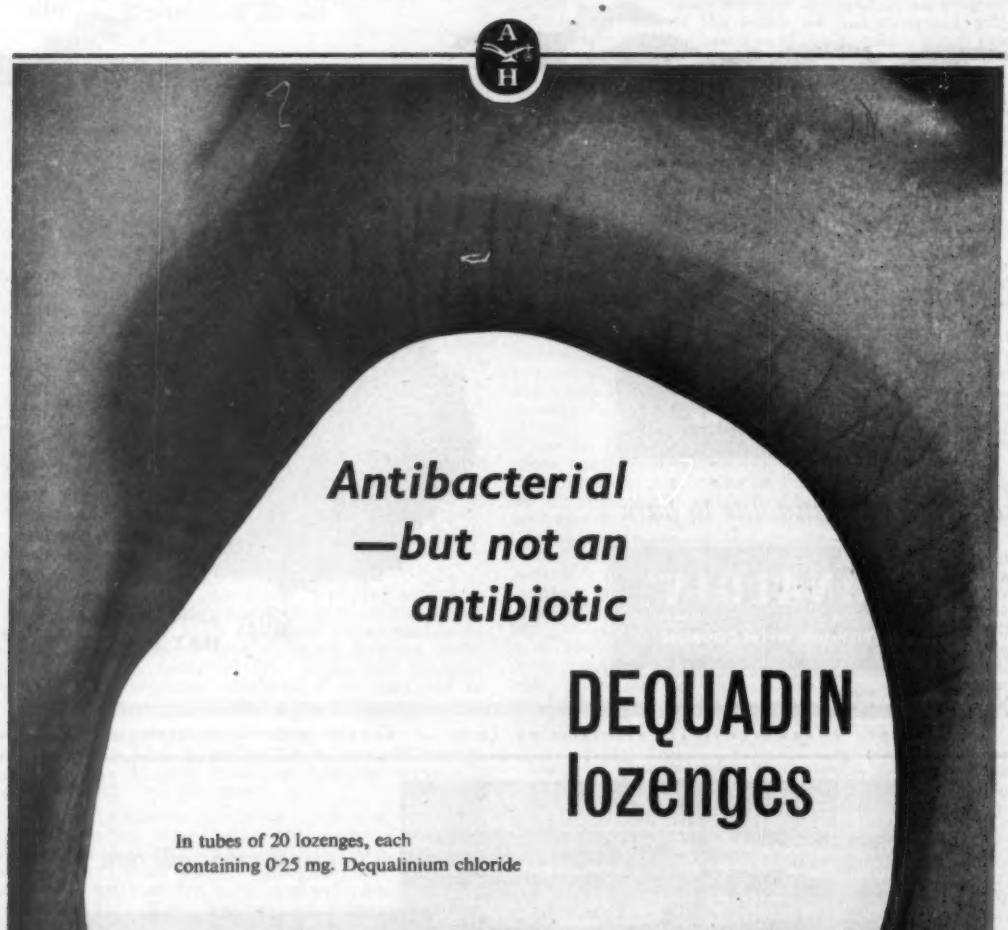
of Cytamen
Sure that each dose is an exact weight of crystalline vitamin B_{12}...
sure that the stated potency cannot vary...
sure that varied response on the part of the patient therefore is not and cannot be due to the product...
sure that you have at your command a range of potencies which allows complete flexability of treatment.
In short, Cytamen provides you with the most therapeutically efficient and the most economical means of combating pernicious anæmia.

CYTAMEN
TRADE MARK
crystalline vitamin B_{12}
50, 100, 250 and 1,000 micrograms per cc.

GLAXO Glaxo Laboratories Ltd., Greenford, Middlesex. BYRon 3434

Subsidiary Companies or Agents in most countries.
In India and Switzerland Cytamen is known as MACRABIN.

27



Antibacterial —but not an antibiotic

DEQUADIN lozenges

In tubes of 20 lozenges, each containing 0·25 mg. Dequalinium chloride

DEQUADIN, a potent antibacterial substance with marked antifungal properties has a wide antimicrobial spectrum. It is non-toxic, and when administered in the form of Dequadin Lozenges it provides effective therapy for common infections of the mouth and throat.

DEQUADIN is not an antibiotic and no cases of sensitivity or the development of resistant strains have been reported following the use of Dequadin Lozenges.

ALLEN & HANBURYS LTD LONDON E 2

TELEPHONE: BISHOPSGATE 3201 (20 LINES). TELEGRAMS: "GREENBURYS, BETH, LONDON"

THE LANCET
LONDON: SATURDAY, SEPT. 28, 1957

Cars and Drivers

OUR highways claim more lives between the ages of one and thirty-five than any single disease. Road accidents have many of the characteristics of a major epidemic, and MCFARLAND and MOORE,[1] of the Harvard School of Public Health, reviewing the findings of a research team, which also included psychologists, anthropologists, and road and car engineers, suggest that doctors can play an important part in combating it.

Some are more liable than others to have accidents, but what underlies "accident-proneness" is far from clear. It is apparently not a physical quality, such as clumsiness, that is open to objective measurement. Accident-repeaters may have an unconscious emotional need or urge to become involved in accidents, and feelings of guilt and craving for attention have, in fact, been found to prevail in such groups[2 3]; but it is all too easy to detect some unresolved conflict, consistent with "proneness," after the mishap. According to the more promising thesis that "a man drives as he lives,"[4] if a man makes mistakes in his personal and social adjustment he will also commit repeated errors in his driving. This was put to the test by comparing the past record of contact with judicial and public-service authorities (including juvenile and adult courts, credit and collection agencies, venereal-disease and public-health clinics, and social-service institutes) of groups of accident-repeater and of accident-free drivers. 66% of accident-repeaters were known to one or more of those bodies, compared with 9% of the accident-free. When "weights" were given to the individual items on the criminal or quasi-criminal records of truck-drivers, and the findings were used to "weigh" members of a new sample, the accident-repeaters could be identified in advance with an accuracy of roughly 80%.[5] "Proneness" would thus resolve itself into something as real but as ill-defined as the "criminal type" or the "inadequate personality"; and like those, for the present, it seems to defy further analysis. When single traits—sensory, psychomotor, or intellectual—are checked against past records of driving accidents, the results are almost uniformly negative. MCFARLAND and MOORE found the correlation between visual acuity and accident-rate in 3000 drivers to be as low as 0·04[1]; and familiarity with the principles of safe driving was reported by some observers to be greater in accident-repeaters than in the accident-free.[6]

The prior detection of physical disorders likely to result in an accident is difficult and sometimes impossible; and their importance may have been often exaggerated in the past. The trigger mechanism of a driver's faint, blackout, or even sudden death, is almost invariably some transient, mild physiological derangement; and such derangements are far more important causes of accidents than long-standing infirmities. From industrial research in this country "skill-fatigue" has emerged as a common and puzzling phenomenon[7]; and drivers are as prone to it as skilled workmen. In the driver its earliest symptom is a slight change in the timing of his reactions; and this is soon followed by a gradual (but to the victim imperceptibe) disintegration of the field of stimuli which normally initiate a coördinated and synchronous set of acquired reflexes. Classically the night-driver halts at an intersection where there is no traffic-light and waits patiently for the green; then, "pulling himself together," he dashes on, intent on a clear roadway ahead and deriving no meaning from the headlights he sees approaching from the side. Skill-fatigue is not necessarily accompanied by physical tiredness; and it cannot be avoided simply by curtailing working hours. MCFARLAND and MOSELEY[5] found that 60% of road-transport accidents were sustained in the first three hours of the journeys. Alcohol has a deservedly evil reputation and is probably second only to skill-fatigue in lowering driving standards.[8] Controlled studies in Sweden have shown that very small quantities significantly increase driving errors committed even by first-class motorists.[9] Indeed, much driving experience and a little alcohol may be one of the deadliest combinations. It is also worth bearing in mind that, though rapidly absorbed, alcohol is eliminated from the body very slowly, and that it may linger in relatively high concentrations in the cerebrospinal fluid and in brain-tissue many hours after the blood-alcohol level has returned to normal. (Most airlines require that pilots shall abstain from alcohol for at least eighteen hours before flying.[10]) None of the popular remedies—exercise, a cold bath, strong black coffee—has the slightest effect on the slowed reactions, impaired judgment, and lack of insight of the alcoholic driver.

It is futile (and it can be very misleading) to study the human elements of road safety with the driver divorced from his *milieu extérieur*. At the wheel instruments become part of his nervous and perceptive system, and controls extensions of his hands and feet. There is no doubt that, with dials hard to read, levers difficult to reach, switches troublesome to operate, seats conducive to bad posture, and obstructions to clear vision, any driver is bound to fail sooner or later; and, if this is plain common sense, many modern cars insult the meanest intelligence. Exhausted perhaps by concentration on speed and power, some designers seem to be oblivious of the simplest facts—for example, that horizontal seat adjustment is no substitute for a vertical range, and that a seven-phase manœuvre (common to many lorries and buses) required to shift the foot

1. McFarland, R. A., Moore, R. C. *New Engl. J. Med.* 1957, **256**, 792, 837, 890.
2. Alexander, F. *Publ. Hlth Rep., Wash.* 1949, **64**, 357.
3. Dunbar, H. F. *Med. Clin. N. Amer.* 1944, **28**, 653.
4. Tillmann, W. A., Hobbs, G. E. *Amer. J. Psychiat.* 1949, **106**, 321.
5. McFarland, R. A., Moseley, A. L. Human Factors in Highway Transport Safety. Boston, 1954.
6. McFarland, R. A., Moore, R. C., Warren, A. B. Human Factors in Motor Vehicle Accidents. Boston, 1955.
7. Bartlett, F. *Brit. J. industr. Med.* 1951, **8**, 209.
8. Health, Medical and Drug Factors in Human Safety. Publication 328, National Academy of Sciences—National Research Council, Washington D.C., 1954.
9. Bjerver, K., Goldberg, L. *Quart. J. Stud. Alcohol*, 1950, **11**, 1.
10. McFarland, R. A. Human Factors in Air Transportation: Occupational Health and Safety. New York, 1953.

from the accelerator to activate the brake pedal is an invitation to catastrophe. But accidents can result from subtler faults. In some cars, presumably for æsthetic reasons, the knobs of several controls are of identical shape and are placed close together on the dashboard: accidents have been caused by drivers, travelling at high speed at night, shutting off the headlights in the belief that they are pushing in the cigarette-lighter. (Similarly, dials hidden behind the steering-wheel may take only an extra 0·1 second to read; but, at 40 miles an hour this represents a distance of 6 feet—possibly the difference between life and death.) Car engineers have made important advances to meet some essential safety requirements; but even these advances are not, as a rule, fully exploited, because they are not tested against the range of human abilities. (Audible warning signals are often tuned with no regard to the diminishing frequencies appreciated by the elderly.) Painstaking measurements of all parts of the human body have been carried out to establish the dimensions of the working space, the location of controls, and the site and shape of instruments necessary for safe driving[11 12]: they are easily available to all and lightly ignored by most. The safety (and comfort) of the driver is also affected by such variables as temperature, humidity, ventilation, carbon-monoxide accumulation, vibration, noise, deceleration and impact force, and, perhaps, most of all, lighting. Some of these present no difficulty in temperate climates; but others, such as carbon-monoxide accumulation, can rarely be excluded as contributory causes of accidents.[13] Very small amounts of carbon monoxide, escaping through small leaks in the exhaust system, or sucked into the car by ventilation, are rapidly absorbed; and they can significantly lower the driver's powers of concentration, interfere with his coördinated thoughts and movements, impair his night-vision, and lull him into mental and physical lethargy. (Concentrations of over 0·1% can be dangerous to life after an hour.) The danger is especially great when carboxyhæmoglobin from other sources is already circulating in the blood: the heavy smoker's may contain 5–8%, which is comparable in its effect on night-vision to driving at an altitude of 8000 feet. In most passenger cars noise and vibration are well within the limits of physiological tolerance; but of many commercial vehicles this is by no means true. The alarming sound-level of 95 decibels has been recorded in some models currently on the road—a noise which might have deafened Lord RODNEY for more than fourteen days.[14] But apart from being a potential cause of temporary or permanent damage to the driver's hearing (and an unmitigated nuisance to the community) such a din is an important contributory source of skill-fatigue.[15 16] Much could be done to combat it by soft mounts, damping compounds, silencers, mufflers, and other devices; and some of these would also reduce vibration, which has been shown to impair visual acuity.[13] Accidents may arise not only from faulty design but from neglect of maintenance. With every mechanical advantage, night-driving is hazardous[17–22]; yet on British roads it is rare to find correctly aimed headlights; and, after many years of unchecked deterioration, some emit so feeble a gleam that the driver is dazzled by approaching lights even when these are properly aimed and are dipped.

Investigations at the Cornell University Medical College[1] have shown that the greatest single cause of death in traffic accidents is ejection of the passengers (irrespective of the speed at which the car has been travelling): indeed, the risk of sustaining any injury, from a moderately severe to a fatal one, is twice as great for a person ejected as for those remaining inside.[23] This particular danger could be effectively reduced—if not entirely eliminated—by safety-belts (especially for the front-seat passenger) and by improved latches and other door-locking devices. The impact of the steering-wheel and post ranks next to ejection as a cause of severe injuries. With so much money spent on so many gadgets, it is remarkable that comparatively simple and cheap safety measures, such as yielding or shock-absorbing steering columns, or even padded dashboards,[24] have not yet been widely adopted. But reproach rests not only with the manufacturers, who might say, as did the "king" to Huckleberry Finn: "Hain't we got all the fools in town on our side? And ain't that a big enough majority in any town?"

Symposium on Nuclear Sexing

THE complaint by Prof. ROBERT PLATT that he had been unable to sleep through a single paper testified to the liveliness of the symposium on nuclear sexing held in London on Sept. 6 and 7 and reported briefly on p. 637 of this issue. Perhaps the first such meeting (as this was) in a new subject is always the most interesting to participants: the excitement of meeting and hearing the real people behind many familiar names of the reprint and the reference list adds zest to the gathering But the continued rapid advances in the subject, and the number of disciplines involved, were more important factors. The seventy participants ranged from cytogeneticists to psychiatrists, from the president of the Royal College of Physicians to an American undergraduate studying at Basle, and from Israelis to Canadians.

From the first session—on the biological and cytological background—the most vivid impression was of the imprecision of our knowledge of the chromosomes of mammals in general and man in particular. It is after all not very reassuring to realise that even the number of chromosomes in man is not certain—though Dr. C. E. FORD was confident that 46, so recently a heresy, would soon be established beyond doubt (apparently the Japanese claim still that most of them have the old number of 48). Again, given that 46 is the normal number in the diploid cells of the testis

11. King, B. G. *Amer. J. phys. Anthrop.* 1948, **6**, 341.
12. Tufts College Institute for Applied Experimental Psychology. Handbook of Human Engineering Data: For Design Engineers. Medford, Mass., 1952.
13. McFarland, R. A., Stoudt, H. W. Physical Variables Influencing Driver Comfort, Efficiency, and Safety. Boston, 1955.
14. Burns, W. *Proc. R. Soc. Med.* 1957, **50**, 222.
15. Broadbent, D. E. *Quart. J. Psychol.* 1954, **6**, 1.
16. Broadbent, D. E. *Proc. R. Soc. Med.* 1957, **50**, 225.
17. Weston, H. C. *Ibid*, p. 176.
18. Smeed, R. J. *Brit. J. physiol. Optics*, 1953, **19**, 63.
19. Harris, A. J., Christie, A. W. Vehicle Headlighting. Department of Scientific and Industrial Research road research paper no. 32. H.M. Stationery Office, 1954.
20. Grime, G. *Proc. R. Soc. Med.* 1957, **50**, 179.
21. Christie, A. W. *Proc. Instn civ. Engrs.* 1954, **3**, 506.
22. Savin, L. H. *Proc. R. Soc. Med.* 1957, **50**, 173.
23. Annual Report from the Commission on Accidental Trauma to the Armed Forces Epidemiological Board. Department of Defence, Washington D.C., 1956.
24. See *Lancet*, 1955, **i**, 440.

(it is not often studied anywhere else), it is not clear how much variation occurs in other tissues. Dr. B. SLIZYNSKI thought, for instance, that variations in sex-chromatin counts from tissue to tissue reflected variations in the number of X chromosomes in the nuclei; and, though his colleagues did not agree with him, it was surprising, to those whose knowledge of chromosomes is derived chiefly from the precise formulations of the genetics textbooks to realise how inexact much of our knowledge on these points remains. The techniques for examining mammalian chromosomes are advancing rapidly, and much may be hoped of the near future. Dr. LEONARD SACHS, reviewing the numerous directions in which nuclear sexing has given food for thought to geneticists, showed how much information could be derived from this single marker of one chromosome pair. Genetics did not advance far beyond simple mendelism till simultaneous exact observation both of inheritance and of chromosome behaviour became possible in a few species. Some of those who attended this session may have been tempted to suggest that the genetics of man, for all its manifold advances, has remained a somewhat rarefied subject, almost a branch of statistical mathematics, largely because the basis of the events it describes has remained beyond the range of direct study: the behaviour of the chromosomes of man has had to be deduced at long range, partially from their effects in inheritance (which are usually complex), partially by analogy from their behaviour in plants and insects, rarely in vertebrates. A science of genetics of man based on direct observation of human chromosomes may well be a very different subject. It may be long in coming; but at least nuclear sexing has given us a glimpse of what it might have to offer.

The later sessions offered a diet of more solid if also more predictable progress in clinical applications. Most time was spent on Klinefelter's syndrome—still, with its picture of a complete sex reversal, the most extraordinary of the new veins opened up by nuclear sexing. Dr. W. M. DAVIDSON is now convinced that the parallelism between the sex-chromatin of somatic cells and the "drumsticks" of polymorphs breaks down in many of these cases, which appear to have female tissues and intermediate polymorphs—an observation probably indicating that the drumsticks are not as closely linked to the XX chromosome pair as is the sex-chromatin. Dr. J. S. S. STEWART described family studies which, among other things, supported the explanation propounded recently in these columns by Dr. DANON and Dr. SACHS [1] (that the sex-reversal depends on the presence of excess of an autosomal masculinising gene which overrides the feminising genes of the X chromosomes) and, moreover, suggested that a similar mechanism is at work in the genetic-male cases. Dr. P. E. POLANI reported satisfactory progress with colour-blindness studies designed to confirm the XX chromosome constitution.[2]

Nuclear sexing has not really added anything, except some firm negatives, to our knowledge of homosexuality or transvestitism: but papers on the subject by Dr. ELIOT SLATER and Dr. C. N. ARMSTRONG, besides being interesting in themselves, provoked a discussion on the legal aspects of nuclear sexing chiefly remarkable for the unanimity of the view that the law should never take any account whatever of the nuclear sex where it conflicted with the externally apparent sex.

Two new syndromes emerged from the symposium. Dr. A. PRADER described two cases of a form of congenital adrenal hyperplasia with deficiency of corticoids and feminisation of male children. This appears to correspond with the much better known and commoner congenital adrenal hyperplasia with virilism, but the essential enzyme deficiency is apparently placed at an earlier stage of steroid synthesis, affecting androgen synthesis in testis as well as adrenal—a most satisfying and original concept. Dr. D. J. B. ASHLEY—singularly pat on Dr. SACHS's demonstration earlier the same day that this was the one thing missing from the spectrum—described what appears to be the first case of complete sex reversal in a genetic male.

All told, this was a very successful meeting. Prof. MURRAY BARR, who wound up the proceedings most happily, cannot but have been proud of the diverse offspring of his original discovery.

1. Danon, M., Sachs, L. *Lancet*, July 6, 1957, p. 20.
2. See Bishop, P. M. F., Polani, P. E., Lessof, M. H. *Ibid*, 1956, ii, 843.

Annotations

TRIALS OF NEW ANTITUBERCULOUS AGENTS

FOR resistant bacilli to develop in a tuberculous patient during treatment is a tragedy. This need happen rarely, if ever, when the three standard drugs are wisely used. So effective are these drugs that there seems to be no place in ordinary practice for relatively untried preparations. Two reports elsewhere in this issue deal with the *p*-aminosalicylic acid salt of isoniazid, 'Dipasic.' This substance is an equimolecular compound of P.A.S. and isoniazid, and a daily dose of 600 mg. contains 300 mg. of P.A.S. This is about a thirtieth of the recognised minimum effective dose when P.A.S. and isoniazid are given together but not in chemical combination. But it is claimed that this combination acts as an independent agent and is actively bacteriostatic against organisms resistant to P.A.S., isoniazid, or both.[1 2] It has also been claimed that resistant bacilli are unlikely to emerge in patients treated with dipasic. The drug seems to have been widely accepted as a remedy.

A group of workers in Edinburgh have lately reported a painstaking investigation with a closely reasoned assessment of the evidence.[3] They found no acceptable evidence that dipasic acts independently of its isoniazid and P.A.S. content, and that its small P.A.S. content probably has little effect either clinically or on the emergence of isoniazid-resistant organisms. This small amount of P.A.S. is, they believe, sufficient to give rise to confusion in in-vitro resistance tests by causing isoniazid-resistant strains of bacilli to appear to be sensitive to dipasic, although patients excreting such strains are unlikely to benefit from the drug. They state that, for practical purposes, treatment with dipasic should be regarded as equivalent to treatment with isoniazid alone. Dr. Dunbar and Dr. Ritchie now report (p. 612) a study of sixteen isoniazid-resistant strains of tubercle bacilli and conclude that resistance to dipasic in vitro closely mirrors that to isoniazid—a conclusion that agrees with the findings of Tinne [4] and Walker et al.[3]

Dr. Allan and his colleagues (whose report appears on p. 609) treated with dipasic 22 patients who had received no previous chemotherapy, and they compared

1. Smith, A. E. W., Wiederkehr, F. X. *Praxis*, 1953, **42**, 884.
2. Brodhage, H. *Science*, 1954, **120**, 998.
3. Walker, W. C., Hay, D., Stewart, S. M., Crofton, J. W. *Tubercle, Lond.* 1957, **38**, 238.
4. Tinne, J. E. *Lancet*, 1956, ii, 252.

the clinical and bacteriological results with similar groups treated with isoniazid and P.A.S., and *o*-hydroxybenzal isonicotinyl hydrazide (' Nupasal—213 ') with or without P.A.S. They conclude that nupasal owes its antibacterial action entirely or almost entirely to the isoniazid liberated in the body. With dipasic a smaller proportion of cavities closed and the bacteriological results were poor; of 17 patients with a positive sputum initially, 8 still had a positive sputum after six months and in 5 the bacilli were resistant to isoniazid.

Judging by these reports dipasic has no advantage over isoniazid. It cannot safely be given alone, and there seems no justification for using it in preference to isoniazid with P.A.S. Its small P.A.S. content is insufficient for its use with streptomycin in a "triple-drug" régime.

Because existing antituberculous agents are so satisfactory, a heavy responsibility rests on firms which market new preparations. But the difficulties of such firms should not be underestimated: efficient and rapid evaluation of a new antituberculous drug calls for greater technical knowledge and resources than are at the disposal of most practising physicians; and coöperative trials require a planning and coördinating agency. Wisely, the British Tuberculosis Association has established a clinical trials organisation,[5] whose objects are "to advise pharmaceutical firms on the use of new drugs in tuberculosis and other diseases of the chest; to arrange clinical trials of substances considered to warrant further investigation, and thereby to ensure that such trials are well planned and fairly and accurately reported." If the new organisation can go even some way towards achieving these objectives it will earn the thanks of manufacturers on the one hand and of clinicians on the other.

CITRIC ACID AND UROLITHIASIS

THE use of citrate to bind calcium in soluble form is so familiar in blood-transfusion that it is surprising that we neglect this function of citrate in considering urolithiasis. The part played by citric acid in stone formation in the urinary tract has received but scant attention since Ostberg [6] postulated that its presence in urine tends to maintain in solution otherwise insoluble calcium salts. Citrate combines with those calcium ions which are freed when a poorly soluble calcium salt is placed in water, thus permitting more free calcium ions to pass into solution; a relatively insoluble salt is thus rendered more soluble by the presence of citrate, and small concentrations of citrate bring about large increases in the solubility of calcium phosphate and carbonate.[7] Albright et al.[8] in fact dissolved bladder stones in 1 patient by instilling citrate solution. Kissin and Locks [9] studied 16 patients with urolithiasis, and found that in 15 the concentration of citric acid in the urine was below 20 mg. per 100 ml., the average concentration being 13 mg. in the patients as opposed to 61 mg. in their control group; total daily excretions were 165·3 mg. and 627·6 mg. respectively. They regarded this deficiency of endogenous citrate excretion as a possible ætiological factor in stone formation.

Various factors influence excretion of citric acid; alkalosis increases output, as does the administration of citrate or citric-acid precursors such as succinic, fumaric, and malic acids; Shorr et al.[10] showed that excretion is under hormonal influence and decreases during the menses; vitamin D increases the plasma level of citrate and therefore the quantity filtered into the urine. Harrison and Harrison [11] found in rats that acetazolamide, a heterocyclic sulphonamide, decreases citrate excretion and impairs the effect of vitamin D, and that calcium phosphate is then precipitated in the renal tubules; if the diet is low in phosphate and high in calcium, plaques form at the tips of the papillary ducts, with stones in the renal pelvis. Gordon and Sheps [12] have observed a patient treated with acetazolamide for three years in whom renal calculi developed. Citrate excretion was much reduced; it returned to normal when acetazolamide was stopped, but was again reduced for twenty-four hours after a single test-dose. Persky et al.[13] report 3 similar cases and suggest that attempts be made to increase citric-acid secretion when acetazolamide is administered. Gordon and Sheps gave acetylsalicylic acid to their patient for three days when he was receiving acetazolamide, but observed no increase in calcium excretion; but the glucuronide mechanism thus invoked [14 15] may not have been stimulated by administration for this short period. Calcium is mingled with the tubular deposit in sulphonamide crystalluria [16]; observation of urinary citrate excretion during treatment with other sulphonamide drugs might therefore prove revealing.

LEFT-HEART CATHETERISATION

CATHETERISATION of the right heart is now a routine investigation in all cardiovascular centres. There was less stimulus to develop techniques for left-heart catheterisation, because the form and level of aortic pulses could be estimated fairly accurately from the brachial artery, and the left atrial pressure could be measured with surprising accuracy by wedging the catheter in a small branch of the pulmonary artery. But the left-ventricular pressure-pulse could not be obtained by these techniques, and consequently the pressures across the mitral and aortic valves could not be measured. The differences in systolic pressure between the left ventricle and aorta, and in diastolic pressure between the left atrium and left ventricle, give the most accurate indication of the degree of aortic stenosis and mitral stenosis respectively. Thus, measurement of pressures in the left atrium, left ventricle, and aorta, simultaneously or in rapid succession, has become important in assessing patients for cardiac surgery.

First, Facquet et al.,[17] in France, and Allison and Linden,[18] in England, measured left-atrial pressures by the transbronchial route. This method is being used extensively at the National Heart Institute in Bethesda, U.S.A. A small plastic catheter is passed through the transbronchial needle into the left atrium and, in 80–90% of patients, can be advanced into the left ventricle without difficulty unless there is appreciable mitral regurgitation. The method is speedy and safe in skilled hands. Hæmorrhage into the pericardium is rare because the left atrium is firmly bound to the bronchus. The disadvantages are the need for the presence of a skilled chest surgeon, and the difficulty in obtaining simultaneously the oxygen-consumption for measurement of the cardiac output by the Fick principle.

Bjork et al.,[19] in Sweden, developed the posterior percutaneous-puncture technique. A long needle is passed from the back into the left atrium—fairly easily

5. British Tuberculosis Association. *Tubercle, Lond.* 1957, **38**, 296.
6. Ostberg, O. *Skand. Arch. Physiol.* 1931, **62**, 81.
7. Greenwald, I. *J. biol. Chem.* 1938, **124**, 437.
8. Albright, F., Sulkowitch, H. W., Chute, R. *J. Amer. med. Ass.* 1939, **113**, 2049.
9. Kissin, B., Locks, M. O. *Proc. Soc. exp. Biol., N.Y.* 1941, **46**, 216.
10. Shorr, E., Bernheim, A. R., Taussky, H. *Science*, 1942, **95**, 607.
11. Harrison, H. E., Harrison, H. C. *J. clin. invest.* 1955, **34**, 1662.
12. Gordon, E. E., Sheps, S. G. *J. Amer. med. Ass.* 1957, **164**, 1215.
13. Persky, L., Chambers, D., Potts, A. *Ibid.* 1956, **161**, 1625.
14. Prien, E. L., Walker, B. S. *New Engl. J. Med.* 1955, **253**, 446.
15. *Lancet*, 1955, ii, 1177; *Ibid*, 1956, i, 1054.
16. Goodman, L. S., Gilman, A. Pharmacological Basis of Therapeutics. New York, 1955.
17. Facquet, J., Lemoin, J. M., Alhomme, P., Lefebole, J. *Arch. mal. cœur.* 1952, **8**, 741.
18. Allison, P. R., Linden, M. V. *Circulation*, 1953, **7**, 669.
19. Bjork, V. O., Malmström, G., Uggla, L. G. *Ann. Surg.* 1953, **138**, 718.

if the atrium is large, but with some difficulty if it is small. In the Fisher[20] modification, which has been adopted by Wood and his associates[21] at the Mayo Clinic, and Goldberg and his associates[22] at the Hahnemann Hospital, the needle is passed into the left atrium under fluoroscopic control. The fine catheter is advanced through the needle into the left atrium, and thence into the left ventricle when possible, while simultaneously the pressure in the left atrium is measured through a side-tube in the needle. The pressure in the aorta can be measured simultaneously by passing a fine radio-opaque catheter up a peripheral artery to the arch of the aorta, or more simply (but with less accuracy) by placing a needle in a peripheral artery. Calculation of the pressure-gradient across a valve has no significance unless the flow is also known, for severe stenosis will produce only a small pressure-gradient across the valve if the flow is small, and a high flow will greatly exaggerate the gradient. The flow is usually estimated simultaneously by Fick's method, using a catheter in the pulmonary artery in the ordinary way. Left-atrial puncture was followed in 80% of Goldberg's cases by a small leak of blood into the pericardial sac, detected only at the subsequent thoracotomy. But a large hæmopericardium with cardiac tamponade has been reported, and in Goldberg's 127 procedures there were 6 cases of hæmothorax and 3 of pneumothorax, and 1 sudden death twelve hours after the procedure. Transient right bundle-branch block is a well-known complication of right-heart catheterisation and, in a patient with established left bundle-branch block, may perhaps cause cardiac arrest. Left bundle-branch block is therefore considered a contra-indication to right-heart catheterisation and perhaps right bundle-branch block ought to preclude left-heart catheterisation.

All these techniques involve the use of long fine catheters, and accurate pressure-pulses can be obtained only from manometers with a small capacity and relatively high frequency-response.

Another direct technique consists in introducing a long needle immediately above the sternum and passing it downwards into the aorta, pulmonary artery, and left atrium.[23] Surprisingly, only 1 case of cardiac tamponade has been reported in 200–300 of these procedures. This method does not give the information which is most wanted from left-heart catheterisation, for the left ventricle is not entered; but it might be useful if right-heart catheterisation was impossible for technical reasons, and it gives more accurate pressure-pulses than are transmitted through a long catheter or through the peripheral arterial system to the brachial artery.

Brock has now shown that pressures across the aortic valve can be measured most simply by direct puncture of the left ventricle through the chest wall,[24] and the information has been assessed by Fleming and Gibson.[25] Simultaneous or immediately successive pressure-pulses were obtained from the brachial artery, and the cardiac output was calculated from the Fick principle simultaneously by means of a catheter in the pulmonary artery. Unfortunately there is no way of measuring the systolic or stroke flow except by dividing the total flow by the heart-rate. While this calculation is accurate for pure stenosis, it is very inaccurate in the presence of regurgitation, when the stroke-flow is greatly increased and the total flow normal or reduced. Thus, a systolic pressure-gradient of 60–100 mm. Hg may be found with dominant aortic regurgitation.[25] Nevertheless this procedure should prove of value in the preoperative assessment of aortic stenosis when the severity is in doubt. While there have been no complications in over 50 of these procedures, there is obviously a risk of ventricular fibrillation in patients with severe aortic stenosis, and the investigation has been done by a surgeon able to proceed immediately to cardiac massage and valvotomy.

20. Fisher, D. L. *J. thorac. Surg.* 1955, **30**, 379.
21. Wood, E. H., Sutterer, W., Swan, H. J. C., Helmholz, H. F. *Proc. Mayo Clin.* 1956, **31**, 108.
22. Bougas, J., Musser, B. G., Goldberg, H. *Amer. Heart J.* 1956, **52**, 359.
23. Radner, S. *Acta med. scand.* 1955, **151**, 223.
24. Brock, R., Milstein, B. B., Ross, D. N. *Thorax*, 1956, **11**, 163.
25. Fleming, R., Gibson, R. *Ibid*, 1957, **12**, 37.

DISCOGRAPHY

THE part played by disc degeneration and disc prolapse in low-back and sciatic pain is often difficult to determine clinically, and routine radiographs are of value mainly in excluding vertebral disease. Indeed no radiographic changes are pathognomic of a posterior disc protrusion. Narrowing of an intervertebral space, which may well indicate disc degeneration, can rarely be assessed on the ordinary film since the views of the spaces are not comparable. In the normal spine certain discs, notably C5/6 and L5/S1, are often narrower than their fellows. Perhaps when the narrowing is unilateral, and associated with vertebral lipping it is more significant, although it may well indicate past rather than present disc disturbance.

In the localisation of disc protrusions and of other space-occupying lesions within the spinal canal, myelography is now well established. In the cervical region (where the neurological signs may be indefinite and surgical exposure is difficult) it permits relatively accurate localisation of a disc protrusion. In the lumbar region, however, it may be misleading, particularly when a large space is present between the dura and the 5th lumbar disc. It was for this sort of case that Lindblom [1] devised disc puncture. A long needle is passed through the spinal canal to the back of the disc; a second, finer, needle is passed through the centre of the first, and the disc is entered, under radiographic control. 0·5–2 ml. of contrast medium is required to display the disc.

The normal discogram presents a bilobular appearance, the contrast medium passing above and below the nucleus pulposus. An irregular spread of dye throughout the whole disc is said to indicate degeneration, while in the presence of a posterior protrusion the material passes backwards and may escape into the epidural space. When a protrusion is present sciatic pain is often produced. In an early series Gardner et al.[2] recorded failure to obtain satisfactory radiographs in 10% of cases, and false-positive results in 15%. In view of the disc damage which has often been reported after lumbar puncture it is interesting that damage to a normal disc during this procedure is very rare, although one example of disc infection has been reported. Gardner et al. consider that disc damage after lumbar puncture is due to infection, and certainly many of the cases follow lumbar puncture during meningitis.

With greater experience, Wise et al.[3] have found that the radiographic diagnosis has been confirmed at operation in 90% of patients. It now appears that the patient's symptoms during the injection may be misleading. Sciatic pain is sometimes felt during the injection of a normal disc, while a large protrusion may be associated with a painless puncture. The normal bilocular character of the disc may be retained in the presence of a posterior protrusion, although in this case the dye is usually displaced backwards. It is in the diagnosis of disc degeneration that most difficulties are still encountered; and it is, of course, with this type of lesion that symptoms and pathological changes are so variable. One of the dangers of discography is that it focuses attention on a lesion which is only part of a more widespread spinal disturbance. Whether it has a place in

1. Lindblom, K. *Acta orthopæd. scand.* 1948, **17**, 231.
2. Gardner, W. J., Wise, R. E., Hughes, C. R., O'Connell, F. B. jun., Welford, E. C. *Arch. Surg.* 1952, **64**, 355.
3. Wise, R. E., Gardner, W. J., Hosier, R. B. *New Engl. J. Med.* 1957, **257**, 6.

diagnosis has still to be seen. Certainly myelography is more informative and should be done first. If the myelogram is normal, and the symptoms suggest disc disease, Wise et al. favour discography rather than surgical exploration.

WEIGHT CHANGES AFTER GASTRECTOMY

PART of the price the peptic-ulcer patient may pay for lasting immunity from pain is persistent loss of weight, which is not uncommon after even partial gastrectomy. Ivy et al.[1] found that in 42% of the cases they collected from published reports the patients had failed to regain their preoperative weight. Everson et al.[2] have reviewed the weight changes in 318 of their patients who were subjected to a Billroth-II type of partial gastrectomy and 118 patients who had vagotomy and gastrojejunostomy. Because weight immediately before operation is liable to be unduly low in patients with pyloric obstruction and high in patients who have taken a strict diet containing much milk and cream, they took the patient's own opinion of his average weight in health. One to eight years after operation 71% of the patients with vagotomy and gastrojejunostomy were underweight (average 16 lb.), compared with 82% of those who had had gastrectomies (average 18 lb.); 15% and 12% respectively were above their original weight; in 13% and 6% respectively weight was unchanged. The amount lost in each group varied up to 84 lb. Weight-loss, then, tended to be commoner and more severe after gastrectomy than after vagotomy and gastrojejunostomy. Muir [3] found that after Billroth-II gastrectomy only 10% of his patients eventually gained weight, and Moore et al.[4] found gains in 27% of their patients. Schmitz et al.,[5] however, found that after a Billroth-I gastrectomy only 34% of their patients lost weight, 43% gained weight, and in 23% weight did not change.

Everson et al. express dissatisfaction with the so-called standard tables of "ideal" or "desirable" weight for height, sex, and age—a dissatisfaction that must be shared by many who have tried to use these tables to judge the variations of measured weights from the average normal. It would be of interest to know how closely these tables, compiled some years ago in North America from measurements of many thousands of candidates for life assurance, compare with similar measurements made today in Great Britain. The large variation about the average in the general population, and the tendency to obesity in the American population causing a skewing towards high values, was pointed out by Keys et al.[6] Undoubtedly, when change in body-weight is used as an index of progress after operations on the stomach, it seems safer to compare the weight immediately before and after operation and at the later examinations with the best and average preoperative weights, when these are known.

It is widely believed that the incidence and severity of loss of weight after gastrectomy is related to the amount of stomach removed, and this belief is clearly supported by the results obtained by Everson et al. What is surprising is that nearly as much weight should be lost nearly as often by patients who were subjected to vagotomy and gastrojejunostomy, whereas after Billroth-I gastrectomies, in which an average of 71% of the stomach was resected, Schmitz et al.[5] found weight-loss only about half as often.

After total gastrectomy few patients regain their normal healthy weight, and many have difficulty in maintaining even a subnormal weight. In this respect leaving even a small rim of stomach, as advocated by Morley and others, is helpful, and even œsophagoduodenostomy seems to be preferable to simple anastomosis to the jejunum. Moreno,[7] dissatisfied with the results from jejunal anastomosis, has used a pouch made of the isolated first loop of the jejunum as a substitute reservoir for the resected stomach. In accordance with suggestions by Hunt [8] and Soupalt et al.,[9] this pouch was interposed between the œsophagus and duodenum. Of 5 patients treated in this way 2 died within three months after operation. Moreno compared the 3 survivors with 2 others in whom total gastrectomy was followed by œsophagojejunostomy, and 1 with a subtotal and 2 with near-total gastrectomies followed by gastrojejunostomy. Body-weight after operation was compared with the average weight for five years before the disease began and ideal weight for age, sex, and height. After operation all the patients lost weight. Part of this loss was usually regained—to the greatest degree by the patients in whom a jejunal reservoir was made after total gastrectomy, to a lesser degree after near-total gastrectomy, and least after total gastrectomy and œsophagojejunostomy—but none of the patients regained the weight they had lost between the onset of the disease and operation. There are several reasons for this failure to regain completely the lost weight. Fat-loss in the stools was abnormally large in each group, but greatest after total gastrectomy, no matter what was the method of reconstituting the continuity of the alimentary tract. Carbohydrate absorption was more rapid in all the patients, and there was obvious hypoglycæmia after glucose-tolerance tests. After total gastrectomy with œsophagojejunostomy, the rapid transit of an opaque meal contrasted notably with the good storage function of those patients in whom a jejunal reservoir was made; some storage was found after near-total resections, but transit of the meal was still rapid.

As might be expected, the capacity for food was greatest when a jejunal reservoir had been made and least after œsophagojejunostomy; there was some gradual increase after near-total gastrectomy. Post-prandial disturbances were least when some of the stomach was left behind, but a jejunal reservoir did reduce their severity compared with direct œsophago-jejunostomy. Although there was some tendency to hypochromic changes in the erythrocytes, there was no consistent abnormality in the total erythrocyte count or hæmoglobin content.

There are several good reasons for preserving some of the stomach if this is possible. A jejunal reservoir does not adequately replace even a small remnant of stomach, and clearly the decision to remove the whole of the stomach should depend on the position of the lesion rather than the technical capacity to make a jejunal pouch. If, however, total gastrectomy is unavoidable, the improvement in food capacity, weight, and general condition when the œsophagus is joined to the duodenum by a jejunal pouch rather than by a direct anastomosis to the jejunum seems to justify the additional operating-time and effort which this step entails. Whether such a jejunal reservoir is superior to one made of the right half of the colon [10] remains to be shown.

Prof. A. A. MILES and Prof. C. H. STUART-HARRIS have been appointed members of the Medical Research Council.

1. Ivy, A. C., Grossman, M. I., Bachrach, W. H. Peptic Ulcer. Philadelphia, 1950.
2. Everson, T. C., Hutchings, V. Z., Eisen, J., Witanovsky, M. F. *Ann. Surg.* 1957, **145**, 182.
3. Muir, A. *Brit. J. Surg.* 1949, **37**, 165.
4. Moore, H. G., Schlosser, R. J., Stevenson, J. K., Harkins, H. N., Olson, M. H. *Arch. Surg., Chicago*, 1953, **67**, 4.
5. Schmitz, E. J., Harkins, H. N., Moore, H. G., Olson, M. H. *Lancet*, 1954, **ii**, 4.
6. Keys, A., Brozek, J., Henschel, A., Mickelsen, O., Taylor, H. The Biology of Human Starvation. Minneapolis, 1950.
7. Moreno, A. H. *Surgery*, 1956, **144**, 779.
8. Hunt, C. J. *Arch. Surg., Chicago*, 1952, **64**, 601.
9. Soupalt, R., Mouchet, A., Causey, M. *J. Chir. Méd.* 1953, **69**, 827.
10. Lee, C. M. *Surg. Gynec. Obstet.* 1951, **92**, 456.

Special Articles

GRAVITY AIR-DISPLACEMENT PRESSURE STEAM STERILISERS

SIMPLE REPAIR OF SOME COMMON DEFECTS *

A. C. SCOTT
M.B. Glasg.
SENIOR HOUSE-OFFICER IN BACTERIOLOGY
From the University Department of Bacteriology at the Western Infirmary of Glasgow

IN a survey of gravity air-displacement sterilisers, Bowie (1955) found serious faults in 59 of 64 examined. There is no reason to suppose that similar surveys in other parts of the country would produce much more favourable results. For example, when twelve gravity air-displacement sterilisers in the Western Region of Scotland were examined during the past year, ten lacked automatic air and condensate discharge, ten lacked a thermometer, three lacked air-filters, and in one steam was introduced at the bottom of the chamber.

Although there is obviously need for a policy of replacement, this cannot be decided quickly because questions governing the optimum design of sterilisers for various purposes have yet to be answered. On the other hand, some inefficient general-purpose instruments can be modified very easily with a great increase in efficiency. The necessary repairs can usually be done by hospital engineering staff in 2 or 3 days, at a cost of £3–5 for materials. It should be emphasised, nevertheless, that the repairs suggested to improve air discharge from the steriliser chamber are applicable only to inefficient general-purpose gravity air-displacement sterilisers of 25 c. ft. capacity or less—that is, the type commonly employed in operating-theatres for the sterilisation of fabrics and gloves. They will not ensure air discharge from larger models and are unnecessary where other means of ensuring complete air discharge exist—e.g., 30-in. vacuum sterilisers—or where failure to remove air completely does not prejudice successful sterilisation, as in the sterilisation of bottled fluids. This paper describes in detail the repair of three general-purpose gravity air-displacement sterilisers with one or more serious defects.

Possible Modifications

Rapid and cheap repair is possible when inefficient sterilisation is due to one or more of the following:

(1) Failure to provide automatic discharge of air and condensate from a correctly sited discharge channel draining from the floor of the chamber.

(2) Lack of a thermometer, preventing accurate control of the exposure of the load to steam.

(3) Superheating from disparity between the jacket and chamber pressures during steaming.

(4) Faulty plumbing connections allowing retrograde contamination of the chamber and contents from the main drains.

In some models it is also possible to repair the ejector system and air-filtering mechanism to increase the safety and rapidity of drying after sterilisation.

Rapid and cheap repair is rarely possible when there is complete absence of a discharge channel draining air and condensate from the chamber floor; faulty placing of the chamber steam inlet allowing steam to enter the chamber at the foot under the trivet; apposition of the chamber steam inlet and chamber discharge port allowing steam to by-pass the load; or complete absence of an air-filtering mechanism allowing recontamination of the load after sterilisation. These faults need long and extensive overhaul by specialised engineering firms; their repair is usually beyond the scope of hospital engineering staff.

Suggested Modifications

Automatic Air and Condensate Discharge

This can be provided by fitting a balanced-pressure, thermostatic trap with a near-to-steam bellows element in the chamber discharge-line. A trap with a near-to-steam element will open when the discharge-line temperature falls 2–4°F below the working temperature. A no-return valve or a hand-operated stop valve, fitted to the discharge-line, will prevent retrograde contamination of the load when a vacuum is applied to the chamber during drying. A strainer fitted proximally prevents debris from lodging in the valve and steam trap and interfering with their function; alternatively a metal mesh filter may be placed in the internal chamber discharge port if this is greater than $^1/_8$ in. in diameter. The distal end of the discharge pipe should drain into a tundish so that an air-break is visible to the steriliser operator; condensate is discharged intermittently during steaming if the balanced-pressure trap is working correctly. Failure to discharge condensate during steaming shows that the discharge-line is blocked, and the sterilising run must be discontinued until it is cleared. A chamber discharge-line modified in this way is shown diagrammatically in fig. 1.

Suitable bellows-type thermostatic traps with near-to-steam elements cost about 40*s*. They can be fitted to the chamber discharge-line by a simple double screw joint and will ensure discharge of air and condensate from sterilisers of 25 c. ft. capacity or less.

Temperature Control

The temperature can be controlled by fitting a thermometer in an unlagged discharge-pipe as near as possible to the internal chamber discharge port. The thermometer element should be housed in a dilatation in the discharge-pipe of at least 1-in. bore so that it is in direct contact with and does not obstruct the flow of air, steam, and condensate leaving the chamber, and so that there is no possibility of air and condensate collecting round it. A thermometer in this position records the lowest temperature in the chamber and can be used for control of the exposure of the load to steam; timing of the sterilisation run is started when the discharge-line thermometer registers 250°F (121°C).

A clock-type bimetallic thermometer, costing approximately 45*s*., may be fitted if the dial can be read easily

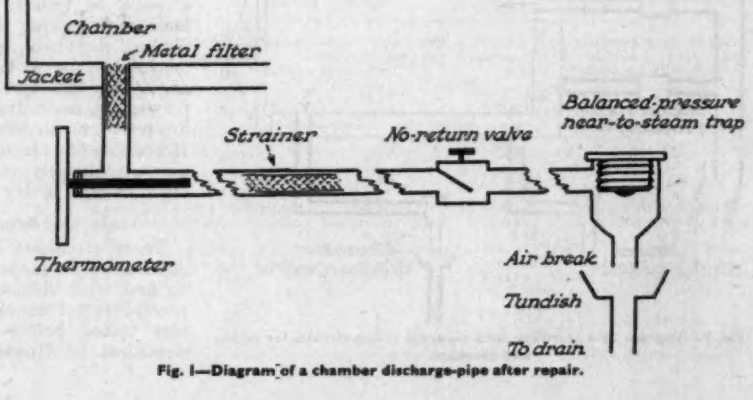


Fig. 1—Diagram of a chamber discharge-pipe after repair.

* A report to the Medical Research Council Working-Party on Steam Pressure Sterilisers.

in situ; if the positioning of the discharge-line makes reading difficult, the use of a mercury-in-steel thermometer with 4–5 feet of capillary tubing allows the dial to be placed so that it is easily visible. If a clock-type thermometer is used, it should be calibrated periodically against an accurate mercury-in-glass thermometer inserted in the discharge-line.

If a recording thermometer is required it should be fitted in addition to a directly-reading thermometer; the element should be housed in a similar manner in the discharge-line and the writing arm set to record the temperature reached in the discharge-line as measured by thermocouple or the directly-reading thermometer.

Superheating

The steam supplied to the steriliser should be dry, as near as possible to the steam-water phase-boundary, and at a pressure of 17 lb. per sq. in. Wetting and superheating in main-steam sterilisers is minimised by passing mains steam, at a pressure of 50–55 lb. per sq. in., through a reducing-valve close to the chamber steam inlet on the steriliser supply pipe. The main-steam pipe proximal to the steriliser supply pipe should be fitted with a pressure-gauge to ensure that the optimum pressure of 50–55 lb. per sq. in. is maintained.

Even with a dry, phase-boundary steam supply, steam in the chamber may become superheated, causing damage to the load and delay in sterilisation, if there is disparity between the jacket and chamber pressures greater than 2 lb. per sq. in. (5°F) during the second half of the steaming period (Walter 1948). This difference is often exceeded in sterilisers with separate steam circuits for both jacket and chamber (fig. 2) and in sterilisers where steam is fed from the jacket to the chamber at a pressure of 20–30 lb. per sq. in. and a reducing-valve has been fitted to the jacket-to-chamber steam pipe to ensure a correct working chamber pressure of 17 lb. per sq. in. (fig. 3).

Where the jacket and chamber steam-circuits are separate, disparity in the pressures may be corrected by alteration of the reducing-valves on the jacket and chamber steam-supply pipes to give working pressures of 17 lb. per sq. in.

Correction of the second type is more difficult; it is necessary to remove the reducing-valve on the jacket-to-chamber steam pipe and reduce the working-pressure of both jacket and chamber to 17 lb. per sq. in. by adjusting the pressure of the steam supply to main-steam models or the pressure control on those heated

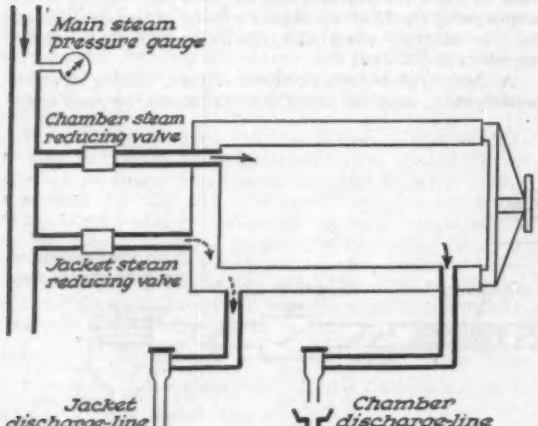


Fig. 2—Diagram of a steriliser with separate steam-circuits for jacket and chamber.

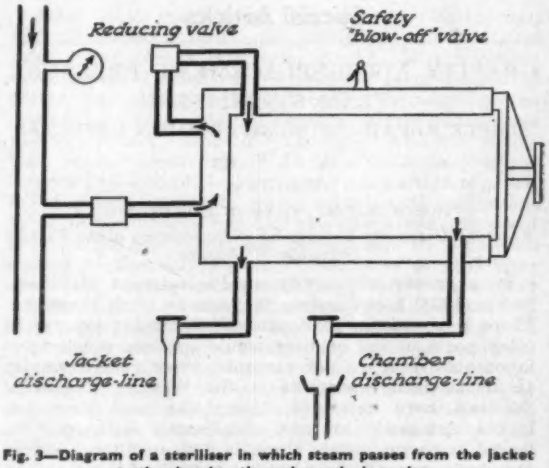


Fig. 3—Diagram of a steriliser in which steam passes from the jacket to the chamber through a reducing-valve.

by gas or electricity. At the same time it is advisable to reset the safety blow-off valve to discharge at 20 lb. per sq. in.; in older gas and electrically heated models, this may be the only way of preventing the working pressure from rising above 17 lb. per sq. in.

The difference between the jacket and chamber working pressures may appear to be greater than 2 lb. per sq. in. because of inaccurate gauge readings. Where possible, the accuracy of the pressure-gauges should be checked periodically against a calibrated test gauge. A siphon fitted to the gauges will protect them against overloading.

Recontamination

Efficient air-filtration is necessary to prevent recontamination whether drying is done by using a vacuum to draw warm, dry, filtered air through the load, or by drawing a vacuum alone and using the air-filter pipe to "break" the vacuum before the load is removed. Although few sterilisers lack an air-filtering mechanism, in many it is deficient or badly maintained. Repair of a deficient air-filter should be attempted; if it should prove impossible, the steriliser ought to be condemned.

An air-break between the chamber discharge-pipe and drain and a no-return valve on the discharge-line will prevent retrograde contamination of the chamber and contents when a vacuum is applied during drying. In sterilisers producing steam by gas or electrical heating of a water reservoir in the instrument, contamination may pass from the chamber to the main hospital water-supply unless there is an air-break between the water-supply pipe and the steriliser filling funnel.

Ejector System

Inability to draw a vacuum for drying may be due to a worn or broken venturi tube; to damaged valve facings or leaking joints in the ejector system; to an air-leak elsewhere, e.g., a loose valve in the air-filtering mechanism or a badly-fitting door gasket; to sharp angles in the ejector-system piping; or to positive pressure in main drains if the ejector discharges into the drain with no air-break. These faults should be corrected. If possible the ejector system should fall to its discharge point, preferably at a condenser. A vacuum of 5–6 in. Hg is enough to dry large loads in 45 minutes.

Tests and Modifications of Three Sterilisers

Three sterilisers have been modified on these lines. After a routine inspection along with the hospital engineer to find what defects were present and to examine the possibility of repair, the efficiency of each steriliser was tested before and after repair by the method described by Howie and Timbury (1956). Test packs

were placed throughout the load to be sterilised in the centre of the dressings bundles; at least one pack was placed in the centre of the largest bundle in the lowest and coolest part of the chamber. Each test pack, made up in small linen dressings-bags, contained:

(1) Browne's sterilisation indicator tubes no. 2. These chemical indicators, if stored below 70°F before use, change colour from red to green in 25 minutes at 115°C.

(2) Steam-permeable envelopes containing swabs contaminated with dust swept from the hospital corridors. The spores in similar samples placed in a laboratory autoclave operated at 227°F (108°C) were killed in 10 but not 5 minutes.

(3) Steam-permeable envelopes containing one-gramme samples of dried, powdered, garden soil wrapped in one thickness of filter-paper. The spores in similar samples placed in a laboratory autoclave operated at 240°F (115°C) were killed in 30 but not 25 minutes.

(4) Six unsterilised dressings swabs, included to test for recontamination during drying.

Note was taken of the jacket and chamber pressures during the sterilisation run, the time used for steaming and drying, the efficiency of the ejector system, the dryness of the load at the end of the run, and the presence or absence of damage to the load from superheating.

After sterilisation the test packs were collected and the dust swabs, earth samples, and dressings swabs were placed in Brewer's thioglycollate medium and incubated at 37°C for at least 96 hours before being considered sterile.

After these tests, repeated if required, the necessary repairs were made by the hospital engineer. About 2 days were necessary to repair each of the three sterilisers. Finally, tests of efficiency were repeated; at the end of the first test-run, drying was done for 45 minutes; the period recommended to the theatre staff for subsequent use was calculated from the state of the load at the end of this time.

STERILISER A

This steriliser is a 1951, horizontal, free-standing, main-steam model. A bellows-type balanced-pressure trap was present on the discharge-pipe but the element was not of the near-to-steam type; it opened 20–30°F below the temperature of phase-boundary steam at the usual working pressure, instead of 2–4°F below, and trapped air and condensate in the chamber. No thermometer was present but there was a blocked screw-fitting for a thermometer at the first angle in the discharge-line. Discharge passed to the drain by an air-break visible to the steriliser operator. The ejector system was capable of drawing a vacuum of 4–5 in. Hg. Plumbing connections were satisfactory. Because this steriliser supplied steam to the chamber via the jacket with no intervening reducing-valve, no disparity was noted between the jacket and chamber pressures.

Dressings were steamed for 45 minutes and dried for 90 minutes, not because this was the time necessary to produce dry dressings, but because this "had always been done." Tests under these conditions showed occasional failure to alter the colour of chemical indicators and sterilise dust swabs, and consistent failure to sterilise earth samples. No recontamination during drying was detected.

In a day a near-to-steam bellows element ('Spirax-Sarco') was placed in the valve seating already present on the discharge-pipe and a clock-type thermometer screwed into the thermometer site at the first angle. A no-return valve was incorporated in the discharge-pipe between the trap and the thermometer.

When test packs were exposed for 45 minutes at a discharge-line temperature of 250°F (121°C), the chemical indicators were altered and the spore preparations sterilised. The load was found to be satisfactorily dry after 40–45 minutes with no evidence of recontamination (see table).

STERILISER B

This steriliser is a 1922, horizontal, free-standing, main-steam model. No automatic trap or thermometer were present on the discharge-pipe; air and condensate were removed by a hand-operated turn valve which was frequently and wrongly kept shut during steaming. A visible air-break was present on the discharge-line. The exhauster system was unable to draw a vacuum for drying of more than 2 in. Hg. An air-filter was present; the plumbing connections were satisfactory, and there was no disparity between the jacket and chamber pressures during the second half of the steaming period. Dressings were steamed for 45 minutes; drying was satisfactory only after 90 minutes. Tests showed frequent failure to alter the colour of chemical indicators and consistent failure to sterilise spores in earth. No recontamination during drying was detected.

During 3 days a balanced-pressure thermostatic trap, strainer, no-return valve, and thermometer were fitted to the discharge-line. The exhauster system was repaired with difficulty enabling a vacuum to be drawn of 5–6 in. Hg.

When test packs were exposed for 45 minutes at a discharge-line temperature of 250°F (121°C), chemical indicators were altered and the spore preparations sterilised. At the end of the first test run, the load was dried for 45 minutes, but despite the presence of the trap to allow discharge of condensate and the increased efficiency of the vacuum system, large quantities of condensate were found lying in the chamber at the end of this period. This was because tilting of the body of the steriliser directed the flow of condensate away from the internal discharge-port: it was corrected by altering the angle of tilt with wooden blocks placed under the steriliser supports. Drying was then satisfactory after 40–45 minutes, with no evidence of recontamination (see table).

STERILISER C

This steriliser, a 1925, free-standing, horizontal, main-steam model with separate steam supply to chamber and jacket, was examined after a report from the nursing

PERFORMANCE OF STERILISERS BEFORE AND AFTER ALTERATION

Steriliser	A		B		C	
Treatment	Fitting near-to-steam trap and thermometer		Fitting near-to-steam trap and thermometer, and repair of vacuum system		Fitting near-to-steam trap, thermometer, and air-filter cup, and repair of vacuum system	
	Before	After	Before	After	Before	After
Discharge-line temperature (°F)	Unknown	250	Unknown	250	Unknown	250
Chamber pressure (lb. per sq. in.)	17	17	17	17	20	20
Steaming-time (min.)	45	45	45	45	60	45
Chemical indicators	2 of 3 unchanged	3 of 3 changed	1 of 3 unchanged	3 of 3 changed	2 of 2 unchanged	3 of 3 changed
Culture of dust swabs	Growth from 2 of 3	No growth from 3 of 3	No growth from 3 of 3	No growth from 3 of 3	Growth from 2 of 2	No growth from 3 of 3
Culture of earth samples	Growth from 3 of 3	No growth from 3 of 3	Growth from 3 of 3	No growth from 3 of 3	Growth from 2 of 2	No growth from 3 of 3
Contamination during drying	None	None	None	None	Heavy; 3 of 3 tests	None in 3 tests
Vacuum (in. Hg)	4–5	4–5	1–2	5–6	1–2	4–5
Drying-time (min.)	90	40–45	90	45	120	40–45
Duration of run (min.)	135	90	135	90	180	90

staff that a load of bandages had caught fire during sterilisation.

No automatic trap was present on the discharge-pipe; air and condensate were discharged through a hand-operated valve which was frequently kept shut during steaming. There was no thermometer. Discharge passed to the drain by an air-break visible to the steriliser operator. Although an air-filter pipe passed through the door, no filter-cup was present; air passed into the steriliser during drying through a wide-mesh metal filter in the base of the filter-cup holder. The ejector system was unable to draw a vacuum of more than 1–2 in. Hg. The plumbing connections were satisfactory. Steaming of dressings was continued for an hour at a gauge pressure of 20 lb. per sq. in., the jacket pressure corresponding; drying was satisfactory only after 2 hours. Tests showed consistent failure to alter the colour of chemical indicators and sterilise earth samples. Recontamination during drying was detected three times; on each occasion, aerobic sporing bacilli and diphtheroids were isolated from the dressings swabs. During 3 days an automatic, balanced-pressure trap with near-to-steam element, clock-type thermometer, and no-return valve were fitted to the discharge-pipe. A new filter cup was fitted to the holder already present and the vacuum system was repaired, allowing a vacuum of 4–5 in. Hg to be drawn.

When test packs were exposed for 45 minutes at a discharge-line temperature of 250°F (121°C) and a chamber pressure of 20 lb. per sq. in., the colour of chemical indicators was altered and the spore preparations sterilised. Drying was found to be satisfactory after 40–45 minutes, with no evidence of recontamination. (see table).

Discussion

Efficient use of steam in gravity air-displacement pressure steam sterilisers depends on free removal of air from the chamber and load before and during steaming. This is achieved by correct packing and arrangement of the load in the steriliser, allowing gravity displacement of air to the foot of the chamber, and subsequent removal of air through a suitably trapped discharge-pipe.

A balanced-pressure trap, if fitted with a near-to-steam element, opens 2–4°F below the temperature of phase-boundary steam, irrespective of the working temperature and can cope with air and condensate discharge over a wide temperature range. A similar type of trap is in use in hospital heating systems, but the element used for this purpose is not suitable for use on a steriliser, for it closes 20–30°F below the temperature of phase-boundary steam; if fitted to a steriliser it closes too soon during steaming and traps air and condensate in the chamber.

Discharge-traps of the metal or fluid expansion type, set to open at a fixed temperature, involve the same risk from closing too soon, trapping air and condensate in the chamber; or they may close so late that maintenance of the chamber steam pressure and temperature becomes difficult. Air and condensate discharge through a hand-operated valve is possible but requires continuous and skilled supervision; this is rarely available.

The increase in sterilising efficiency due to efficient air removal is shown by the results obtained from steriliser A where repair was limited to the replacement of the heating-system element present in the trap by a near-to-steam element, and the fitting of a thermometer.

If a balanced-pressure trap with a near-to-steam element is present, attempts to remove air by drawing a vacuum before steaming are unnecessary. Satisfactory air removal by this method requires a vacuum of 30 in. Hg; few sterilisers can produce a vacuum of this order unless fitted with a special pump. Drawing a fore-vacuum, though it may remove some of the air present in the chamber, does not allow secondary and later removal of the air which is displaced from the load during steam penetration, and by causing superheating may delay sterilisation and damage the load. Efficiency of the ejector system in gravity air-displacement sterilisers is necessary only to increase the rapidity of drying; a high vacuum is not needed for this purpose.

The inadequacy of the chamber pressure-gauge as a means of controlling sterilisation is shown by comparison of the chamber pressure-gauge and discharge-line temperature readings in the table. In the presence of complete air discharge, the discharge-line temperature in each steriliser during steaming was 250°F (121°C); the simultaneous chamber pressure-gauge readings were 17 lb. per sq. in., 17 lb. per sq. in., and 20 lb. per sq. in., corresponding to theoretical chamber temperatures of 254°F (123°C) and 259°F (126°C). This discrepancy was due to fatigue in the gauge springs producing high readings; it can also be due to faulty housing of the thermometer element in the discharge-line. The inaccuracy of pressure-gauge readings as a guide to the chamber temperature is increased if air discharge is incomplete, because the presence of air in the chamber lowers the temperature without altering the working pressure.

For these reasons a thermometer is necessary, and the practice of controlling sterilisation by pressure-gauge readings is to be condemned. If a recording thermometer is fitted it should be calibrated against the temperature reached in the discharge-line during steaming as measured by thermocouple or a directly-reading thermometer. If, as is common, the recorder writing arm is set to record temperature by inference from the chamber pressure during steaming, it does not produce a true record of the chamber temperature.

Although an accurate and correctly sited thermometer records the lowest temperature in the chamber, it gives no direct indication of the efficiency with which steam penetrates the load. Routine tests with indicators of known heat resistance are therefore necessary, particularly as steam penetration depends largely on the nature of the load and the way in which it is packed and placed in the steriliser. Chemical indicators placed in the centre of each bundle allow a rapid check on correct packing and placing; if the indicator is not altered the bundle should be withdrawn from use, repacked, and resterilised. Bactericidal tests with spore preparations give final proof of the steriliser's biological efficiency (Savage 1954), but the results may be misleading unless the preparation is of known resistance to moist heat, placed in the centre of the individual bundles, and in such a form that steam can penetrate it easily. Spore tests carried out with unstandardised material incorrectly placed in the load may mask inefficient sterilisation.

During drying, efficient air-filtration is necessary to avoid recontamination of the load with airborne organisms. The method of testing described, with test packs placed in the centre of the bundles being sterilised, demonstrates heavy contamination which has escaped filtration in the surrounding fabrics. Under these conditions a pad of sterile cotton-wool or gamgee in the filter cup prevents recontamination provided it is changed daily and does not become wet from back-flushing of steam along the filter pipe. A commercially produced clay filter may be fitted, but this also filters inefficiently if wet.

Sterilisation depends on the correct operation of satisfactory equipment (*Lancet* 1956). Ignorance or carelessness may endanger life: the life of the operator as a result of accident when attending to the steriliser (e.g., by opening the steriliser door before the chamber pressure gauge has returned to zero); or the lives of patients by producing unsterile loads. Staff responsible for working sterilising equipment should be trained in the principles of modern steam sterilisation and the operation of the particular instrument with which they work. Perkins (1956) has written an authoritative account

of modern gravity air-displacement sterilisation practice and equipment.

Summary

Many inefficient operating-theatre dressings sterilisers could be modified usefully and easily in 2 or 3 days at a cost of about £5 for materials.

Three cases are presented to show increase in efficiency after correction of common faults.

To ensure sterilisation, correct training of staff is as important as efficient equipment.

I wish to thank the hospital engineer, Mr. J. Wood, for carrying out the necessary repairs, and for technical advice.

REFERENCES

Bowie, J. H. (1955) *Pharm. J.* **174**, 473.
Howie, J. W., Timbury, M. C. (1956) *Lancet*, ii, 669.
Lancet (1956) ii, 979.
Perkins, J. J. (1956) Principles and Methods of Sterilisation. Springfield, Ill.
Savage, R. M. (1954) *J. appl. Bact.* **17**, 278.
Walter, C. W. (1948) Aseptic Treatment of Wounds. New York; p. 61.

MEDICAL DEFENCE UNION

SPEAKING at the annual meeting of the Union on Sept. 17, Dr. S. COCHRANE SHANKS, the president, said that last year membership continued to increase; and, though the number of cases referred to solicitors was steady at under 300, more and more members were asking for help and the office was busier than ever; moreover, in damages awarded and claims settled the sums tended to increase. For these reasons an increase in the subscription would be necessary; the year covered by the report showed a deficit.

In their annual report the council draw attention to the difficulties which arose in a case where the Union accepted responsibility for the legal representation of a member against whom proceedings were threatened. But the member left the country and did not renew his subscription, and the Union was obliged to tell the hospital authority concerned that it could no longer nominate a solicitor to act in the case, because the member was out of benefit. The moral, says the report, is that doctors engaged by hospital authorities should be required to belong to a defence body and to continue membership (including, if necessary, overseas membership) after leaving the hospital, since the Statute of Limitations runs to three years.

The council welcomes the Medical Act of 1956 in general, but plans to give evidence to the British Medical Association's committee reviewing the operation of the Act.

The total membership of the Union at the end of 1956 was 43,251, including 2741 elected and 173 reinstated during the year.

Symposia

NUCLEAR SEX

THIS symposium, the first to be devoted to the subject, was held at King's College Hospital Medical School, London, on Sept. 6 and 7, and was attended by some seventy members from ten countries.

Cytological and Genetic Aspects

Dr. B. SLIZYNSKI (Edinburgh) wondered why the sex chromatin is usually reported to be present in only 60–80% of nuclei in women: if it represents the XX chromosome pair and this pair is present in all female nuclei, it should never be absent. He suggested that Timomen's data, which indicate gross variation in chromosome number from cell to cell in most tissues, could account for this. In subsequent discussion, however, both Timomen's data and the invisibility of sex chromatin from some female nuclei seemed generally to be regarded as the result of technical defects.

Dr. C. E. FORD (Harwell) showed how limited is present-day knowledge of human chromosomes, but was optimistic concerning the prospects of advance with new techniques. He discussed especially the evidence for the relatively new view that the human chromosome number is 46, and the pairing of the human X and Y chromosomes, which is end to end or sometimes does not occur at all. He also undertook to make available, to all interested, directions for handling biopsy material (chiefly testicular) likely to be suitable for chromosome studies in intersexes.

Mr. J. L. HAMERTON (London) described the behaviour of the large and relatively easily studied sex chromosomes in *Rattus natalensis*. In them normal pairing, with chiasma formation, of the homologous segments of the X and Y chromosomes seems definite, though it has been denied in mammals with smaller sex chromosomes; and Dr. L. SACHS (Rehovoth, Israel) in discussion, was very sceptical of its occurrence in man.

Mr. H. P. KLINGER (Basle) had studied the sex chromatin in amnion and chorion of human embryos. Amitosis, common in these cells, is preceded by division of the sex chromatin and nucleolus; and it was possible to follow the stages of this division in detail.

Dr. CECILIE LEUCHTENBERGER (Cleveland, Ohio) had estimated desoxyribosenucleic acid (D.N.A.), arginine, and dry mass of large numbers of single spermatozoa of bull and man, and emphasised the constancy of D.N.A. content of fertile sperma.

Dr. SACHS discussed the extent to which the contributions of nuclear sexing to the study of human sexual anomalies were of interest to geneticists. The majority of the cases appeared to be of genetic origin, though the mode of inheritance was not always clear. The different modes of action of abnormal genes were well exemplified in this field: thus a gene might appear to act directly on the developing gonad (Turner's syndrome, perhaps Klinefelter's also), on a well-defined stage of steroid synthesis (adrenal virilism), or on the tissue response to hormones.

Dr. P. RIIS (Gentofte, Denmark) described a series of changes in the early stages of tissue-culture of lymphocytes whereby the small deep-staining nuclei enlarged and acquired a much looser texture, so that the sex chromatin became readily visible and these normally unsexable cells could easily be sexed.

Intersex and Related States

Dr. SACHS, on behalf of Dr. MATHILDE DAMON (Rehovoth, Israel) discussed the rôle of the sex chromosomes in human intersexes. The feminine phenotype without normal gonads might develop in the presence of any sex chromosome constitution, certainly with XX and XY, possibly with XO, possibly with XX/XO chimaeras, and so on. An almost normal male phenotype with testes might develop in the presence of XX chromosomes (Klinefelter). The converse to this is a sex reversal in the opposite direction, a normal feminine phenotype with ovaries in the presence of XY chromosomes—had not yet been described. [Dr. Ashley's contribution later in the meeting filled this gap.] The pseudohermaphrodites in which gonads and sex chromosome constitution corresponded could now be fairly readily understood, but complete sex reversal of the Klinefelter type still presented a major problem, as did the early stage, the actual gonadal anomaly, of Turner's syndrome.

Dr. A. PRADER with Dr. R. SIEBENMANN (Zürich) described two cases of congenital adrenal hyperplasia with adrenal deficiency and feminisation. This new syndrome appears to correspond in a general way with adrenal virilism, but to represent an enzyme deficiency at a still earlier stage of steroid synthesis than the latter condition.

Prof. C. OVERZIER (Mainz) pointed out that in ordinary cases of so-called gonadal agenesis (Turner's syndrome) a rudiment of the gonad is in fact demonstrable. He had seen two cases of total agenesis of the gonad, and in both of these wolffian and müllerian ducts developed to a limited but equal extent. His hypothesis of "initial and permanent induction by the gonads" accounted for these findings, which are at variance with the accepted hypothesis, based on Jost's gonadectomies in embryos, of the course of development in Turner's syndrome. Prof. A. JOST, however, in discussion, found Professor Overzier's theory unacceptable without experimental confirmation.

Dr. E. SLATER (London) confirmed the absence of any anomalies of genetic sex among homosexuals. In an extensive study of the kinship of homosexuals and other sexual deviants the only certainly significant findings had been the late position of male homosexuals in the sibship and their birth to older mothers.

Dr. C. N. ARMSTRONG (Newcastle upon Tyne) discussed transvestitism, in which also no anomalies of nuclear sex had been found. He emphasised the early origin and depth of the feelings involved, and the difficulties of formulation of any policy for dealing with these cases.

Dr. W. M. DAVIDSON with Dr. D. ROBERTSON SMITH (London) discussed the sex nodules ("drumsticks") of polymorphs, with special reference to Klinefelter's syndrome. This provided the only suggestion of discrepancy between nuclear sex determined by other methods, and polymorph sex. In cases which were genetic females by all other methods, intermediate figures were obtained with polymorphs. Graphic methods showed that this discrepancy did not depend on any anomaly of polymorph nuclear lobing.

Prof. H. R. WIEDEMANN (Krefeld) had used the polymorph method successfully in study of a very large series of intersexes, the data generally confirming those of users of more conventional methods. Collected data of drumstick frequencies in females of differing ages suggested a steady fall in frequency with age.

Dr. B. LENNOX with Dr. M. A. FERGUSON-SMITH, Mr. W. S. MACK, and Dr. J. S. S. STEWART (Glasgow) described the findings in a large series of Klinefelter's syndrome (or congenital micro-orchidism, as they wished to re-christen it) derived chiefly from a male infertility clinic. He emphasised the significance of differences in testicular morphology between male and sex-reversed female cases. Their statistics showed the syndrome to be a major cause of male infertility: the true frequency of genetic-male and genetic-female cases was probably at least 1 : 10,000 each in Glasgow.

Dr. SIEBENMANN described the testicular morphology of genetic-females in Klinefelter's syndrome in greater detail, emphasising the small tubules and the deficiency of elastic tissue. 7 cases of dystrophia myotonica with testicular deficiency had all proved to be genetic males.

Dr. STEWART with Dr. FERGUSON-SMITH, Dr. LENNOX, Mr. MACK, and Miss MARION IZATT presented data on the families of the cases of Klinefelter's syndrome in which the high proportion of childless uncles strongly suggested a pattern of inheritance with paternal transmission of genetic-female and maternal transmission in the genetic-male cases. Anomalous Rh serological findings suggested at least the possibility of triplication at the E locus. He believed that the mode of inheritance supported the autosomal masculinising gene explanation of the syndrome, and presented a more detailed hypothesis involving translocation of chromosome segments.

Dr. P. E. POLANI with Dr. P. M. F. BISHOP (London), Dr. FERGUSON-SMITH, Dr. LENNOX, and Dr. STEWART presented an interim report on colour-blindness in Klinefelter's syndrome. Though many more cases will be needed to reach statistical significance, the figures to date (no colour-blindness cases in 19 tested genetic females and 4 in 26 genetic males) already suggest that nuclear sexing accurately represents the XX/XY constitution of these patients.

Discussion on these papers centred largely on the nature of the genetic defect in sex-reversed cases of Klinefelter's syndrome: not all speakers accepted the Glasgow group's contention that 'genetic-male cases form a group equally well defined and equally interesting. Danon and Sach's explanation, based on the action of an autosomal masculinising gene, was generally accepted as the best yet available.

Dr. D. J. B. ASHLEY (Liverpool) presented a case in which feminine habitus and genitalia were present, and the nuclear sex was male. Normal-looking ovaries were present, and their normality was confirmed by biopsy. Though Professor OVERZIER entered a necessary caveat that biopsy might not exclude an ovotestis, this is probably the first reported case of complete sex reversal in a genetic male.

Study of Tumours

Dr. A. S. TAVARES (Porto, Portugal) had confirmed that well-differentiated tumours conformed to the sex of the host, but that many teratomas in the male were "Barr-positive." He believed that there existed a special group of "undifferentiated-cell" tumours in which intermediate counts were obtained. Pure seminomas were always male, but seminomas arising in teratomas had the same sex as the teratoma.

Dr. N. B. ATKIN (London) had studied sex-chromatin, and chromosomes in squash preparations of human tissues. Of 65 suitable tumours from women, 50 had single sex-chromatin bodies, 7 two, and 8 none. The two-body nuclei were probably all tetraploid, chromosome counts and D.N.A. estimations agreeing in this: in 1 case at least this character persisted in serial biopsies over several months.

Dr. LOIS MYERS (London) had sexed 105 teratomas. The 64 teratomas from women were uniformly female. The 41 from men included 13 uniformly female and 8 mixed male and female. In the mixed cases the areas with male and female nuclei were mixed together at random, with abrupt transitions from one to the other. In discussion, though Dr. LENNOX defended his hypothesis of origin of teratomas by fusion of haploid cells, the cytologists and geneticists present preferred Dr. TAVARES's suggestion of the reduplication of the chromosomes of a single haploid cell. Dr. MYERS was unconvinced by either explanation.

In conclusion, Prof. MURRAY L. BARR (London, Ontario), who presided at this last session, himself drew together many of the divergent strands of the symposium. Especially interesting was his historical survey showing how a war-time interest in air-crew fatigue had led through a study of chromatolysis in cat hypoglossal nuclei to the recognition of the sex-chromatin body, and to the opening up of the many lines of research indicated in the symposium.

The Wellcome Foundation, the Ciba Foundation, and King's College Hospital Medical School contributed to the costs of this symposium.

Letters to the Editor

INFLUENZA

SIR,—There has been a tendency both in the lay and in the medical press in recent months to emphasise the mildness of the influenza which has appeared in this country with increasing frequency in the past few weeks and has been active in the East for some considerable time. It is of course true that no good will come of undue alarm, much less panic. Has there not, however, been too much of an ostrich policy in this matter?

Experience of the past 150 year swould suggest that a pandemic of influenza is fully due, since an interval of nearly 40 years has elapsed since the last one. In these matters memory appears to be rather short: the first wave of the influenza of 1918–19 which appeared in the early summer of 1918 was quite mild; its only alarming feature was its remarkable infectivity; but the second wave which struck from October to December was grim and formidable to the last degree.

No conclusive proof of the activity of a virus in the pandemic of 1918–19 was made while it lasted, although its existence was suggested repeatedly. Since the pioneer work of Smith, Laidlaw, and Andrewes,[1] however, a vast amount of valuable work of great scientific interest has been done in many countries on the rôle of virus in localised epidemics of influenza. It may be assumed that since the rôle of virus in these epidemics has been so clearly demonstrated it must follow that a pandemic is due to a virus of peculiar invasive power. This may well be the case; but we do not know. Still less do we know whether such a virus would be more or less easily controlled by prophylactic inoculation of virus vaccine than the epidemic strains already referred to.

We do know, however, that by the end of the last pandemic the great majority of competent bacteriologists were convinced that *Hæmophilus influenzæ* had played an important part in the pandemic. Much of this evidence was summarised by McLeod et al.[2]

It has been shown by Laidlaw [3] that the virus produces a highly infectious but not particularly severe disease in the ferret and can be adapted to mice so as to produce a fatal disease with characteristic lesions. It is only in the pig, however, that a spontaneous disease resembling human influenza in its combination of high infectivity and severity has been observed and produced experimentally. Lewis and Shope's experimental work,[4] however, showed very clearly that this disease depended on the combined action of a virus and a hæmophilus bacterium.

It is not, therefore, stretching probabilities to suppose that the *H. influenzæ* is responsible for the most formidable features of pandemic influenza although it may depend on the virus to open the bronchial tree to its attack.

In this connection the paper by Duval and Harris [5] deserves consideration. Working in New Orleans in the autumn of 1918, at the height of the pandemic which was producing 2000–3000 cases per diem in that city, they tried prophylactic inoculation with a vaccine which contained *H. influenzæ* and nothing else. This was prepared mainly from the Wollstein strain of the Rockefeller Institute. A saline suspension was prepared from 48-hour cultures on a blood-agar which was prepared with 1% of washed human red cells, and this suspension was sterilised by 10–15 minutes' exposure to chloroform. It was given subcutaneously in three doses which contained 10^9,* $10^9 \times 0{\cdot}5$, and 10^8 bacteria respectively and at three-day intervals. 30% of sharp reactions were recorded but these did not exceed in severity those which often follow T.A.B. inoculation and rarely occurred after the second or third injections.

This vaccine was tested on employees of banks, business houses, &c. In 342 volunteers who received three doses, there were no cases. In 238 refusing inoculation, there were 93 cases and 27 pneumonias.

Taking all the inoculated, whether they had one dose or more, and including cases which occurred in a recrudescence two months after the first epidemic wave, the results were: 3072 inoculated, 3% of illness; 866 not inoculated, 41% of illness.

These are more convincing results than any that I know to have been published for virus-vaccine control of influenza and they were carried out in the circumstances most likely to provide a severe test of any measure of prophylaxis.

It seems to me, therefore, that they deserve more careful attention from those responsible for the health of the community than they appear to have had.

A grave mistake may well be made at the present time by restricting observation and prophylactic effort to virus.

Department of Clinical Surgery,
University of Edinburgh. J. W. MCLEOD.

"PNEUMOCONIOTIC NEUROSIS"

SIR,—On the last morning of the recent course on industrial diseases at Hammersmith Hospital a round-table discussion was held on the working of the Industrial Injuries Act in relation to pneumoconiosis. The present situation has many anomalies; men with severe respiratory disablement who have worked in the pits for years have their claims rejected, while others with no functional impairment are awarded sums on a quite extraordinary percentage basis which appears nonsensical to those who make the assessment. Wide divergencies exist in the proportion of claims accepted by panels in different parts of the country and the psychological effect on the men appears to be most pernicious; amongst other things the medical profession is made to look ridiculous.

Clearly the rigid terms of the Act are out of keeping with reality. Medical thought in the past has been confused and too much attention is still being paid to purely static X-ray appearances; the living individual and his functional impairment are forgotten while heated argument develops over radiological shadows as to which particular label should be attached to the condition. Attention is riveted on minutiæ.

In conversation with industrial medical officers and other informed persons at this excellent meeting, one could not but sense the intense frustration of the present position; it was clear also that those who have to administer the regulations often find them almost unworkable and that conflicting interests further bedevil the situation. All this is neither good administration nor good medicine. Could not a commission of inquiry be appointed to give an independent report?

Clare Hall Hospital,
South Mimms,
Barnet. NORMAN MACDONALD.

TREATMENT OF MIGRAINE

SIR,—Dr. Leyton's letter of Sept. 14, claiming that migraine is "a definite organic complaint," is not very convincing to a chronic disbeliever like myself, particularly as I gave four references by other workers to support my "psychosomatic" viewpoint, and he has given five of his own reasons for his "organic" assumption.

Dr. Leyton claims that he helps over 80% of his patients by purely organic methods and not suggestive

1. Smith, W., Andrewes, C. H., Laidlaw, P. P. *Lancet*, 1933, ii, 166.
2. McLeod, J. W., Ritchie, A. G., Dottridge, C. A. *Quart. J. Med.* 1921, 14, 327.
3. Laidlaw, P. P. *Lancet*, 1935, i, 1118.
4. Lewis, P. A., Shope, R. E. *J. exp. Med.* 1931, 54, 349, 361, 373.
5. Duval, C. W., Harris, W. H. *J. Immunol.* 1919, 4, 317.

* In the original paper a billion and assumed to be the U.S.A. billion ($=10^9$).

methods—but his methods *are* highly suggestive, if, for example, the administration of chorionic gonadotrophin has to be "kept up for years . . . every three days."

Dr. Leyton is to open a discussion for the Hypnotherapy Group on migraine, at 1, Wimpole Street, on Oct. 17 at 8 P.M., when both sides of the argument can be heard. Any reader who is interested would be very welcome.

London, W.1. GORDON AMBROSE.

INADEQUACY OF GENERAL ANÆSTHESIA FOR ABDOMINAL OPERATIONS

SIR,—Both Dr. Loder (Sept. 7) and Dr. Pelmore (Sept. 21) appreciate that irritation of autonomic nerves contributes to operative shock.

Dr. Loder's suggestion that this can be prevented by infiltration of the appropriate autonomic plexuses with local anæsthetics is sounder on theoretical grounds than the use of ganglion-blocking agents.

Animal experiments have shown that the non-specific responses and vasomotor collapse which follow irritation of autonomic nerves do not occur if the area is infiltrated beforehand with a local anæsthetic.[1] Ganglion-blocking drugs confer no similar protection and have no curative value.[2] Chlorpromazine confers a high degree of protection if given at the same time or slightly before the autonomic disturbance.[3] Two general anæsthetics, hydroxydione and pentobarbitone, have a protective action approximately half that of chlorpromazine.[4]

Even if one makes reservations about the application of the results of animal work to clinical problems, it is more reasonable to follow up positive findings than to advocate a method that finds no experimental support.

London, S.W.18. D. A. BUXTON HOPKIN.

NERVOUS SYSTEM IN PORPHYRIA

SIR,—In your annotation of Sept. 14, you seek to explain the neurological lesions of acute porphyria through the action of a toxic agent. Your suggestion that this is the Waldenström porphyrin seems unlikely in view of the work of Cookson and Rimington,[5] who concluded that this substance was an artefact derived from porphobilinogen by chemical means. In fluorescence studies on necropsy material, my colleagues and I,[6,7] like others, have failed to discover any increase in porphyrin in the brain, the results even suggesting a reduction in the normal coproporphyrin content. The view that acute porphyria is due to poisoning with porphobilinogen or uroporphyrin is of course no longer tenable, but it seems undesirable to postulate a hypothetical toxin, as you do, to explain some of the details of the histopathology. The chief element in the neuropathology of the disease is demyelination. Since myelin is maintained and replaced by processes which most probably involve tetrapyrrollic enzymes, it is surely more profitable to search for a cause of impaired myelin production in the disordered pyrrol metabolism of the patients than to look for a *deus ex machina* in the form of an abnormal toxic condensation product of porphobilinogen, which might destroy myelin.

It is unnecessary also for the understanding of the local vasoconstrictor effects often seen in the disease to postulate the presence of a humoral pressor agent, even if there were a suitable pyrollic candidate for this rôle. The relationship of the vascular phenomena to the lesions of porphyria has been discussed elsewhere.[6,7] The resemblances between the lesions of porphyria and those known to be due to localised vascular obstructions are of a non-specific kind. The view that vasospasm is the primary mechanism in the disease dates back to old experiments with large doses of hæmatoporphyrin, conditions which are not found in the disease. Although this theory has been copied, with modifications, from one paper on the subject to another, it has not received confirmation on the way.

Finally, I should like to plead for the retention of Waldenström's classification of the disease into the chronic, the acute, and the cutanea tarda types. Watson's classification into erythropoietic and hepatic groups, so widely used in America, has undoubtedly helped to distinguish the rare chronic from the other types, but it overemphasises the importance of the liver lesions in the commoner acute type. In the latter, functional and structural alterations in the liver are generally slight, though in porphyria cutanea tarda they are often of clinical importance.

Queen's University, Belfast. JAMES B. GIBSON.

INSTRUMENT FOR TAKING SPECIMENS FOR CERVICAL CULTURE

SIR,—In the investigation of sterility, it is important to reveal the presence of bacterial infection in the cervix. Symptomless pathogenic bacteria are an important factor in the resistance of the cervical mucus to sperm invasion, even when the husband has apparently normal semen.[1]

Cultures made from a high vaginal or posterior-fornix swab are often valueless, since many commensals are grown and the important pathogen in the cervix is not discovered. Taking a cervical culture is not easy, since the risk of vaginal contamination must be avoided and the cervical plug itself is, in these cases, very tenacious, difficult to extract, and often quite scanty. Some success was attained by the insertion, under direct vision through a 'Cold-lite' speculum, of a platinum wire direct into the cervix; this was plated directly on the culture media. But many cultures were reported negative in this process, and it was found much preferable to remove the whole cervical mucus plug and transmit it direct to the laboratory without dilution by broth or other medium. This has been done by the use of specially designed 'Pyrex' tubes (made for me by James Woolley Ltd., Manchester), with orifices of diameter varying from 2 to 4 mm. for use according to the viscosity of the secretion of the cervix. Into each tube is inserted a rubber bulb, originally designed for Ryle's tubes, which can exert very strong suction. Using the cold-lite speculum, the glass tube is inserted directly into the cervix without touching the vaginal walls; the whole of the cervical mucus plug can be extracted and transferred directly to a dry sterile container, which may be transported to the laboratory with very little loss. The method has been in successful use for nearly ten years, and the number of positive results has almost doubled since it was adopted.

Culture of the cervix at the appropriate time in the menstrual cycle has revealed the cause in a number of puzzling cases of sterility. Appropriate treatment for the pathogenic organism has often been followed by a conception soon afterwards.

Infertility Clinic,
Manchester Victoria
Memorial Jewish Hospital. BERNARD SANDLER.

1. Sandler, B. *J. Obstet. Gynæc., Brit. Emp.* 1952, **59**, 203.

1. Reilly, J., Compagnon, A., Tournier, P., Du Buit, H. *Vie méd.* May, 1955.
2. Tardieu, G., Pocidalo, J. J., Himbert, J. *Bull. Soc. méd. Hôp. Paris*, 1954, **70**, 497.
3. Reilly, J., Compagnon, A., Tournier, P. *Ann. Méd.* 1954, **55**, 5.
4. Abernathy, R. S., Halberg, F., Spink, W. W. *J. Lab. clin. Med.* 1957, **49**, 708.
5. Cookson, G. H., Rimington, C. *Biochem. J.* 1954, **57**, 476.
6. Gibson, J. B., Goldberg, A. *J. Path. Bact.* 1956, **71**, 495.
7. Gibson, J. B., Parkes, W. E., Brennan, C. F. *Irish J. med. Sci.* 1957, **6**, 127.

CONSULTANT AND SPECIALIST

SIR,—Relatives of so-called "chronic" mentally ill persons will strongly approve of Dr. Bickford's letter (Sept. 14) about Dr. Rowland Hill's reference to "medical custodial work in chronic psychiatric institutions." Certainly, we of this Association, wholeheartedly endorse Dr. Bickford's views.

It seems, however, that there are grounds for the layman to conclude that Dr. Bickford is one of only a small minority of doctors who do not conform to the traditional outlook of custodial detention and of acceptance of inevitable chronicity in a vast number of mental-hospital patients. I quote, for example, from an article in the summer number of *Mental Health*, wherein Dr. O. Fitzgerald, of Shenley Hospital, writes: "The other three quarters [of the total residents of a mental hospital] are regarded by the doctors and nurses as utterly unresponsive to any specialised form of medical or nursing skill. This latter fact is concealed. Such is the life of fantasy we lead in the mental hospital world."

One infers from Dr. Rowland Hill's assertion that he believes doctors of inferior status and ability are good enough for the "chronic" mental patient. If this is, in fact, what he is saying, then I assure him his attitude will be deeply resented by their relatives, among whom, as I well know, there is a strong upsurge of opinion that, by and large, the "chronic" patient is not receiving the medical attention his affliction warrants.

It is also relevant to quote here the views of a senior physician of a mental hospital [1]:

> "Psychiatric practice in a mental hospital has for too long been the favoured career of doctors with inadequate personalities, or who lack the average quantum of drive and energy. Until even ten years ago there was little in the way of active treatment to bother such people. Many sought and found a sheltered life. But recent changes have produced much that would encourage the keen, healthy, young doctor with a zest for active work. Some, but not enough, are opting for psychiatry."

Is it surprising that relatives deduce that the primary cause of the deterioration of patients is (as, indeed, has now been admitted by the Ministry of Health [2]) inadequate medical and nursing care rather than mental disease?

I, therefore, in the name of my Association, advance the plea that Dr. Rowland Hill and all other members of his profession recognise the medical needs of the 130,000 "medically uninteresting" patients in this country's mental hospitals.

T. YEADON
Vice-chairman,
Skipton, Yorks. Friends of Menston Hospital.

THE WOLFENDEN REPORT

SIR,—May I thank Dr. Learoyd for his common-sense criticisms of the Wolfenden report (Sept. 14)? He very rightly says that "in the rôle of law-makers or arbiters of morals many . . . psychiatrists are not convincing." Unhappily this truth is increasingly disregarded. As to both homosexuality and murder it should be appreciated that the provision of treatment is not the primary duty of the law. The law exists also, and perhaps primarily, to control the environment in the interests of the life of the community. I submit that the courts should abandon claims to deal with homosexuality and murder as problems in morals or therapy, and should rather consider them as problems in social surgery. The surgeon does not enter into futile debate as to the rights of the malignant cell to its own way of life. He makes the practical judgment that it is a danger to the life of the whole body, and on that basis he deals with it. So also with the murderer, or the homosexual, it is not for the courts to weigh too nicely the responsibility of the individual, to split hairs in the light of psychological theory, or the McNaughten rules, but rather to exercise the practical function of protecting the community.

Dr. Learoyd points out the danger that implementation of the recommendations of the Wolfenden report would lead to the growth of groups of homosexuals, analogous to the local infiltration of a tumour; to that the individual body reacts by encapsulation, and similarly the community reacts by imprisoning its abnormal elements. An individual assailed by a homicide or by a homosexual may use such force as is necessary for self-protection, and the question of the absolute responsibility of his assailant does not deprive him of his right of self defence. The rights of the community are the sum of the rights of its individual members, and it is logical that the community as a whole may take necessary measures to guard itself by encapsulation (that is imprisonment) or excision (that is, execution), according to the degree of gravity of the attack, or the radical nature of the action necessary to safeguard the life of the community.

Accrington. R. C. WEBSTER.

APARTHEID IN NURSING

SIR,—By the passing of the Nursing Act (1957) the South African government has taken a further step in the implementation of its apartheid policy. In terms of the new Act non-white nurses are effectively deprived of a share in the decisions of the Nursing Association, and in general are placed in the position of second-class nurses (for example, white nurses may not now, except in cases of emergency, be given orders by any non-white nurses, even if senior in the profession). In addition the existing (multiracial) branches of the association have been dissolved and replaced by separate branches for "white," "coloured," and "native" nurses; however, only the whites have any real say in the affairs of the association (section 33 [3]: "A decision of the majority of the members of the Association present at any meeting held under this Act, by members who are white persons, shall constitute a decision of the Association").

Control of nursing in this country is vested in the South African Nursing Council. Under the new Act no non-white person may serve on the council. Separate registers for nurses of different races are prescribed in the Act, and it is laid down that the council may prescribe different uniforms, qualifications, and conditions for registration for nurses of different racial groups. Several present members of the council have already (in evidence to a government select committee) expressed the opinion that this type of discrimination is desirable.

It will be seen that the provisions of the new Act are completely in accord with the principles of apartheid, but are in marked contrast with the International Code of Nursing Ethics.

What has been the reaction of South African nurses to this legislation? Mass meetings of nurses have been held all over the country in protest, and resolutions attacking the principles of the Bill were passed at many centres. Public multiracial demonstrations have also been held and protest marches have taken place in Johannesburg, Cape Town, and Durban.

Non-white nurses at numerous places (including the 4 largest centres, Johannesburg, Cape Town, Durban, and Port Elizabeth) have gone further. At these places nurses have refused to be party to the formation of separate branches, and have not elected committees to run the branches called for in the Act. It will be noted that this is not defiance of the law but an entirely legal and dignified gesture.

There is a widespread feeling that the Nursing Association, as now constituted under the Act, cannot possibly represent the nurses of this country adequately, nor protect their interests in the way it ought. Accordingly,

1. *Spectator*, April 5, 1957.
2. Report of the Ministry of Health for 1955, pp. 122, 123.

nurses in Johannesburg, after numerous requests from all parts of the country, have called a national conference of nurses to meet there in November. This conference will discuss the legal, professional, and ethical implications of the new legislation, and will consider measures designed to protect professional standards. Among other possibilities is the formation of a multiracial organisation of nurses.

The conference will, of course, be open to all nurses in contrast to any conference called by the Nursing Association in terms of the Act. It is laid down that only white nurses may attend a meeting, petitioned for by members of the association. It should also be noted that a multiracial organisation formed at the conference would not be limited in its activities and procedure in the same way as the association is restricted by the Nursing Act.

Orlando Municipal Clinic, Orlando, Johannesburg, South Africa.

G. KHALA
Organising Secretary of the National Conference of Nurses.

A NEW DISEASE ?

SIR,—Dr. Thomas (Sept. 21) asks for enlightenment upon a small point regarding the actual word which gives syphilis its name.

He has made the laudable error of consulting the first edition of the poem (Verona, 1530) which unfortunately is notoriously corrupt: there are several misprints and in one place two whole lines dropped out. Two editions appeared in the following year (1531). One (Rome) has the two missing lines but did not correct "Syphilidenque"; the other (Paris) was beautifully printed from the Verona edition without the two missing lines but with misprints corrected and so it has the correct "Syphilidemque." Subsequent editions vary according to which of these three is followed: for instance, the second Italian edition (Bologna, 1738) is copied from the corrupt Verona edition and so omits the two lines while retaining the misprint in an unfamiliar word.

But why bother? Sensible people let sleeping dogs lie, and the medical profession might reasonably let "dead" languages die.

Oxford. H. M. SINCLAIR.

HIGH-PRESSURE OXYGEN AND RADIOTHERAPY

SIR,—The letters of Dr. Sanger (Aug. 24) and Dr. Targowsky (July 27 and Sept. 14) raise points of great theoretical interest. Perhaps, therefore, one more theoretical suggestion will not be out of place.

It is known that cancer cells derive a greater proportion of their free energy from glycolysis than from respiration in contrast with normal cells.[1] Respiration proceeds at higher rH values than glycolysis. The action of raised oxygen pressure is probably to raise the rH of the tissues; cancer cells would therefore be expected to be more vulnerable under these conditions, as seems to be the case if the good results from high-pressure oxygen and radiation therapy are confirmed.

It is worthwhile, therefore, examining the ways by which, theoretically, the rH of the tissues might be raised. Now as $rH = 2(Eh/C + pH)$,[2] the rH of the tissues could theoretically be raised either by increasing the pH of the tissues—that is, by inducing an alkalosis or by increasing the Eh of the tissues (in other words, by inducing a condition which I have called an "oxidosis"[3]). The ways of producing an alkalosis are well known. It has been shown that both ascorbic acid and glutathione given in massive doses intravenously cause a substantial fall in the Eh of the tissues (about 150 millivolts)[4]—a reductosis—and so it might be expected theoretically that such substances as alloxan and dehydroascorbic acid given intravenously might produce a rise in Eh of the tissues—an oxidosis.

The theoretical deduction to be drawn from these facts is that if an alkalosis were induced and then an oxidosis superimposed by the administration of a substance such as dehydroascorbic acid the conditions in the tissues caused by increased oxygen pressure could be imitated.

These theoretical suggestions can easily be checked by the following experiments:

(1) Measure the Eh and pH of blood under varying oxygen pressure in vivo and in vitro and hence deduce if the changes in rH deduced actually occur.

(2) Measure the change of Eh in the tissues and of the blood in vivo after the administration of such substances as dehydroascorbic acid and alloxan.

Blackheath, London S.E.3. G. E. LOXTON.

CLASSIFICATION OF GASTRIC ULCERS

SIR,—May I suggest that the pain usually associated with a ptosed hypochlorhydric stomach can, fluoroscopically, be seen in the erect position to be situated centrally and not in the body of the stomach and that it is caused by the dragging of the stomach on the lesser omentum (hepatogastric and hepatoduodenal ligaments). The pain is relieved by the horizontal position because it abolishes the pull of gravity, and therefore is mechanical, and not chemical as is tentatively suggested by Mr. Daintree Johnson (Sept. 14, p. 518). It is questionable, therefore, whether partial ablation of the stomach however modest, can be considered as the appropriate treatment for this condition when medical means are available which restore the tone of the gastric musculature.

London, W.1. J.-JACQUES SPIRA.

A VIBRATING BED FOR ANKYLOSING SPONDYLITICS

SIR,—It is not uncommon, in taking the histories of patients with ankylosing spondylitis, to find that constant gentle agitation in sleep prevents much of the morning stiffness and pain which is characteristic of this condition. Sleeping on a yacht at anchor, in aeroplanes, and in railway carriages have all been noted to have this ameliorating effect. Some two years ago, we therefore designed and made a vibrating bed to give constant gentle agitation to the spine of the sleeping spondylitic.

A $^1/_3$-horse-power motor (single phase, 1440 revs. per minute) was bolted to a plate and suspended by welded struts under the frame of a hospital type bed (see accompanying figure). Coil springs were welded at intervals of about 9 in. to the underside of a spring frame, and the other end of the coil was welded to the top side of the bed frame; thus the spring frame which carries the patient is suspended

The small $^1/_3$-H.P. electric motor fitted to the underside of an ordinary hospital bed. It runs off the normal electrical power-point.

1. Warburg, O. Metabolism of Tumours. London, 1930.
2. Dixon, M. Multi-enzyme Systems. Cambridge, 1951; p. 64.
3. Loxton, G. E., Le Vay, D. *J. Pharmacol.* 1954, 6, 178.
4. Loxton, G. E., Le Vay, D. *Nature, Lond.* 1953, 171, 524.

from the bed and held by these coils. A solid bar was welded across the spring frame and to this a shaft was secured and connected to a pulley shaft, slightly off centre. This pulley shaft was driven from the motor by a 'V' belt drive. Pulleys on the motor shaft give some variations in speed. This is a prototype, and we are now proceeding to make a similar bed which will run more silently and which is geared to give greater control of the rate of vibration.

After sleeping on this bed the spondylitic is less stiff and painful in the morning and is able to start his daily work with less discomfort and at an earlier hour than without its use.

Westminster Hospital, London, S.W.1. F. DUDLEY HART
H. J. RIDGEWAY.

FAINTING AND CEREBRAL DAMAGE

SIR,—Dr. J. G. Bourne is to be congratulated upon his excellent article (Sept. 14) and, indeed, upon his continual efforts to draw attention to some of the dangers of dental anæsthesia. My purpose is not to criticise Dr. Bourne's main argument but to mention one or two points that have occurred to me while reading his paper.

In two and a half years, Dr. Bourne has discovered 14 fatalities in the course of dental anæsthesia. In 1952 general dental anæsthesia was administered to 23 persons per 1000 of the population.[1] At the 1951 Census the total population was 53,327,000. If these figures are considered to be applicable to the period commencing October, 1954, then, during Dr. Bourne's review, 3,166,000 dental anæsthetics were administered, with a mortality of 1 : 226,000. In two London teaching hospitals, at which records stretch back for thirty-two years, 1 death has occurred in a (conservatively) estimated total of 400,000 administrations.

The inferences to be drawn from these figures are, firstly, that the present method of dental anæsthesia, with all its imperfections, is comparatively safe, and that attempts to introduce other methods should not be made without due consideration. Secondly, there is no cause for complacency, for the figures suggest that the mortality can be reduced by almost half. Attention should here be drawn to Dr. Bourne's 10th case, in which a dental practitioner extracted twenty-five teeth under general anæsthesia with no other aid than that of a receptionist.

Dr. Bourne suggests that danger may be avoided, or reduced, by the use of the supine position and by a method of nitrous-oxide anæsthesia which avoids anoxia.

The supine position is dangerous in outpatient dentistry, for the reason that there is an increased risk of the patient inhaling saliva, blood, and even teeth. It must be remembered that the inhalation of quite small amounts of blood may cause death; indeed, this is the most likely cause of death in Bourne's 9th and 10th cases, in both of which bloodstained fluid was found in the lungs after the extraction of fifteen and twenty-five teeth respectively. The recumbent position is obviously the correct treatment for the danger of "fainting"; it is so easy to cope with one danger at the cost of introducing another which is no more remote.

The avoidance of anoxia is entirely desirable. In this connection it is curious that Dr. Bourne has made no mention of Dr. Arthur Tom's very important paper.[2] Briefly, Dr. Tom found that the stage of surgical anæsthesia is unnecessary for the extraction of teeth, that adequate operating conditions can be provided by a combination of analgesia and amnesia ("amnalgesia"), and that this state can be produced by means of nitrous oxide and a high proportion of oxygen. In my experience, the method is a good one, though not suitable for every case.

But the true answer to the problem is quite different. All forms of anæsthesia are potentially lethal—just as driving a car is potentially lethal. No person should be permitted to administer an anæsthetic unless he has been trained to do so, is aware of the problems that may be encountered, and is possessed of the requisite knowledge to deal with those problems. Nor should safety be sacrificed to expediency. Unless this point of view is accepted, the type of fatality suggested by Dr. Bourne's 10th case is bound to occur and can only be regarded as a deplorable hazard.

Otford, Kent. F. F. CARTWRIGHT.

1. Report of the Ministry of Health for 1952. Part II: On the State of the Public Health. H.M. Stationery Office, 1953: p. 150.
2. *Brit. med. J.* 1956, i, 1085.

POLYTHENE AND POLYVINYL TUBING FOR BLADDER CATHETERS

SIR,—I should like to support Mr. Cosbie Ross and his colleagues (Sept. 14) in their advocacy of 'Polythene' or polyvinyl catheters when prolonged bladder drainage is required.

I have long been interested in the treatment of vesico-vaginal fistula, in which steady and efficient bladder drainage for 10 or 14 days after operation is so important. In these cases the usual rubber catheter (including the Foley catheter) has the disadvantage of causing urethral irritation or worse; and often there is a tendency for urinary salts to form and to block the lumen. On both these counts the "plastic" catheter is superior; and on only one occasion out of many scores have I seen any appreciable "salt" deposit.

The tubing can be easily cut from the roll, and extra "eyes" made, as Mr. Cosbie Ross and his colleagues described. I prefer, for the type of case I have to deal with, to anchor the catheter by a stitch placed deeply in the anterior lip of the external urinary meatus; the thread has previously been bound firmly, but not tightly, to the plastic tube at the precise level which will enable the end to project freely into the bladder but not so far as to impinge on and irritate the opposite wall. Polythene tubing (no. 4 size) is suitable for thin catheters used for a urethral repair, and polyvinyl tubing (no. 5 D size) for other types of case.

The Radcliffe Infirmary, Oxford. J. CHASSAR MOIR.

CARDIAC CATHETERISATION

SIR,—Dr. Paton in his comments of Sept. 14 on priority claims for the introduction of cardiac catheterisation has put in a strong plea for the recognition of Prof. Frederick W. Pavy who, in 1858, reported on the use of this technique "as early as February, 1854." He was, as Dr. Paton pointed out, studying some of the fundamental aspects of carbohydrate metabolism. He was, in fact, largely reporting on experiments in which he checked some of the findings made by Claude Bernard, confirming most of them, but taking issue with some others.

In Leçons de Physiologie Expérimentale Appliquée á la Médecine, which Bernard gave at the Collége de France, and which were published in 1855, he described his experiments in detail. In the fifth lecture (Jan. 9, 1855) on "distribution de la matière sucrée dans l'organism" he mentioned the withdrawal of blood from the right heart in a living dog through "une sonde en métal" (reproduced in fig. 6, p. 119), a procedure, which he called "une sorte de cathéthérism cardiaque." (Pavy had called it ". . . a process, so to speak, of cardiac catheterism.")

The impression is gained on reading both the abstract of Pavy's paper before the Royal Society and his Lettsomian lecture that the technique of cardiac catheterisation occurred to him independently of Claude Bernard. Both men were then working on similar problems of carbohydrate metabolism, and the simultaneous withdrawal of blood from the right heart and the carotid artery in the living animal was crucial to their work.

Bernard did not state when he first performed "cardiac catheterism." But, in any case, the priority of publication would seem to be his.

Faculty of Anæsthetists, Royal College of Surgeons of England, London, W.C.2. GERALD R. GRAHAM.

PREVENTION OF MATERNAL DEATHS

SIR,—The problem of priorities in booking for hospital confinement, described by Dr. Egan in her letter of Sept. 14, arises in many places. In this area it is solved by making "provisional" bookings for patients who are low on the priority list. These women are then referred to their family doctor to continue antenatal supervision, and are given an appointment to attend the hospital clinic at the thirty-fourth week of pregnancy. By that date it is usually possible to decide whether hospital confinement is advisable on medical grounds, and, if not, whether any beds are likely to be available after allowing for late booking of cases in the higher priority groups. If no bed is available, there remains ample time to arrange for home delivery under the supervision of the family doctor who has already carried out the early antenatal care.

Boston, Lincs. R. F. LAWRENCE.

DEFICIENCY OF AN EXTRA-THYROID ENZYME IN SPORADIC CRETINISM

SIR,—Some of the comments in Professor Querido's letter (Sept. 7) necessitate a reply, especially the criticism implied in his statement "a valid clinical observation showing that hypothyroidism may be unresponsive to thyroid powder and react favourably to treatment with triiodothyronine would provide important information upon a controversial issue." Our clinical observations are perfectly valid. In brief, a child aged 4 years 3 months failed to respond adequately to dry thyroid *B.P.* but was converted to a completely normal child by *l*-triiodothyronine. No question arises of the inadequate supervision of the oral administration of dry thyroid, which was given in hospital for 56 days of the 119-day period of thyroid treatment, during which time the daily dose reached 20 grains. Several different batches of dry thyroid were used during the first 56 days of treatment, some of which had been shown to be effective in other patients. That the dry thyroid was absorbed in the intestine is strongly supported by the changes in temperament, pulse-rate, and weight which followed treatment although the signs of cretinism were not materially affected.

In common with most investigators in the United Kingdom we are unable to have the serum-protein-bound I^{127} estimated as a routine in our patients, which explains the absence of serial estimations. The explanation of the low pre-treatment serum level of protein-bound I^{127} is clear from the data given in the case-report. The only thyroid tissue present was ectopic and quantitatively inadequate. The thyroid uptake of I^{131} was low. Indeed, at first we accepted that dysgenesis of the thyroid gland was the complete explanation of the cretinism. Failure to respond satisfactorily to dry thyroid revealed that this was not so.

We were more cautious with our conclusions than Professor Querido indicates. We were, in fact, careful *not* to conclude that in our patient the unresponsiveness to dry thyroid but reversal of the cretinous state by *l*-triiodothyronine was proof of the deficiency of an extra-thyroid enzyme. We merely postulated that "the hypothyroid state of our patient may represent the results of such a deficiency." Perhaps when this child is older it may become a reasonable proposition to attempt to elucidate this problem. Meanwhile, with her excellent progress further radioactive-iodine studies appear unjustified.

It is, of course, correct, as Professor Querido points out, that the first definite in-vitro demonstration of absent enzyme activity in thyroid tissue was made in his laboratories in a case of goitrous cretinism which lacked dehalogenase activity. The hypothesis that goitrous cretinism is due to intrinsic defects, probably enzymatic in origin, at different stages in the synthesis of the thyroid hormone had, however, previously been made with reasonable confidence by others, including two of the present authors. That this hypothesis was justified despite Professor Querido's scepticism is evident from the subsequent accumulated experience of many workers including, in particular, the excellent work of Professor Querido with Stanbury and others on dehalogenase.

We reiterate our belief that the postulate that an inborn deficiency of an enzyme concerned in the peripheral extra-thyroid deiodination of thyroxine to triiodothyronine may sometimes lead to hypothyroidism which does not respond to dry thyroid but responds to *l*-triiodothyronine merits serious consideration.

J. H. HUTCHISON
G. C. ARNEIL
Royal Hospital for Sick Children, and Royal Infirmary, Glasgow. E. M. MCGIRR.

CYSTOSCOPY IN THE INVESTIGATION OF POST-MENOPAUSAL BLEEDING

SIR,—The investigation and management of the patient with postmenopausal bleeding whose uterus has been proved empty by curettage is one of the more interesting aspects of gynæcology. Now that vaginal cytology can be used to supplement the curette there may be fewer occasions when a malignant diagnosis remains in doubt. But there will always be a number of women who are doubtful as to the orifice through which blood has emerged, and I know of one aged spinster in whom curettage involved such technical difficulty that an innocent uterus was eventually removed instead of her bleeding hæmorrhoids.

Mr. Dewhurst and Dr. Dutton (Sept. 14) remind gynæcologists to use the cystoscope in all doubtful cases, but there is one danger which should be pointed out. In the absence of any demonstrable pathology of the bladder there will not unnaturally be an inclination to exonerate the urinary tract as the site of the offending hæmorrhage. This false sense of security following cystoscopy recently delayed the diagnosis of a malignant renal tumour in a deaf patient whose hæmaturia had originally been classed as postmenopausal bleeding.

Birmingham. W. G. MILLS.

INSULIN IN EARLY SCHIZOPHRENIA

SIR,—In recent years you have published a series of articles sometimes critical of the value of insulin therapy vis-à-vis other treatments of early recoverable schizophrenia. These articles aroused much discussion and dissension, and they undoubtedly caused some psychiatrists to question anew whether or not it was still necessary to use insulin therapy in the treatment of early recoverable schizophrenia.

The penalty for a wrong decision in the treatment of a case of early recoverable schizophrenia, and the omission of any treatment helping to bring about recovery, may mean thirty years of intense suffering in the back wards of a mental hospital for the individual patient concerned. Few decisions on treatment in medicine, therefore, carry such disastrous sequelæ if they happen to be the wrong ones.

The 2nd International Congress for Psychiatry was held in Zürich from Sept. 1 to 7. A special meeting of those interested in physical treatments in psychiatry was arranged to discuss "the changing indications of the various somatic treatments in psychiatry." Not unexpectedly to me, there turned out to be absolute unanimity amongst the speakers chosen to represent various countries that the use of insulin coma was still desirable in selected schizophrenic patients, and should certainly not yet be abandoned. It was felt, however, that the advent of the new chemical tranquillisers did help some patients previously treated with insulin coma and so reduced the need for insulin-coma treatment in some

patients. Also, none of the speakers thought that electro-convulsive therapy was an adequate substitute for insulin coma in all patients.

The following took part in the discussion: L. B. Kalinowsky (United States, chairman), M. Mueller (Switzerland), W. Sargant (Britain), E. Stroengren (Denmark), L. Bini (Italy), J. J. Lopez Ibor (Spain), W. von Baeyer (Germany), and P. H. Hoch (United States). W. Mayer-Gross (Britain) and P. Pichot (France), who had also been invited to take part but were unable to do so, later also found themselves in agreement with these unanimous views of all the other speakers about insulin. The variety of countries represented and the unanimity of viewpoints expressed should, I think, make us now hesitate before being too ready to give up insulin treatment as of possible help in some early recoverable schizophrenic patients.

London. WILLIAM SARGANT.

CARDIAC ARREST DURING HALOTHANE ANÆSTHESIA

SIR,—Dr. Kay (Aug. 24) is, of course, quite right when he states that anæsthesia with a calibrated vaporiser has its pitfalls for the unwary. He has, however, somewhat oversimplified the problem. Thus, his assumption that the blood and central-nervous-system concentrations of anæsthetic drugs lag far behind the alveolar-air content, is true only of di-ethyl ether.[1] Where a drug passes readily through the alveolar membrane and is not unduly soluble in blood or tissues, there is in fact very little protecting lag in the build-up of the concentration of the agent in the central nervous system and in the heart. Halothane is almost certainly an agent of this type. For Raventos [2] has shown that the blood-level changes very rapidly with changes in concentration of the inhaled drug. Further, the quick recovery which follows its clinical use confirms that there is, with small percentages at least, very little tendency for a large store of the drug to accumulate in the tissues. It is, therefore, far more important when halothane is being given to limit the amount used to the patient's immediate requirement and not to pursue a vigorous "over-pressure" technique comparable to that which gives such good results with ether.

Halothane is extremely volatile at ordinary room-temperatures. The result is that relatively enormous percentages of it can be suddenly delivered by uncalibrated apparatus. When such large amounts of the drug escape into a closed circuit the result may be the rapid development of profound respiratory depression, severe cardiac inhibition in the inadequately atropinised subject, and dramatic fall in blood-pressure. Indeed, it seems almost certain that all the deaths which have occurred so far during halothane administration have, in fact, been due to the employment of excessive concentrations, and for this reason the calibrated vaporiser is infinitely preferable.

The high volatility of halothane at room-temperatures is, as would be expected, combined with a sharp variation with small changes in temperature. Falkner Hill [3] has shown, for example, that with the administration of the drug in an ordinary Boyle bottle the temperature of the halothane can fall 13°C over 8 minutes with an accompanying decline in delivered halothane concentration from nearly 5% to 2·5%. Such extreme changes in temperature inevitably involve considerable alterations in the depth of anæsthesia. An anæsthetist experienced in the use of his own apparatus will no doubt learn to compensate for these changes, but for the less skilled the resulting disturbances can be very confusing.

It will, therefore, be appreciated that the plea for the use of a calibrated vaporiser does not rest on a facile assumption that a given percentage of halothane always produces the same pharmacological change in all individuals. Such an apparatus does, however, ensure that the amount of the drug administered is kept within safe limits and prevents the inhalation of an overwhelming overdose in two or three breaths. It thus contributes much both to the safety and to the smoothness of the anæsthesia.

The Royal Infirmary, Manchester. A. R. HUNTER.

1. Hunter, A. R. *Brit. J. Anæsth.* 1956, **28**, 244.
2. Raventos, J. *Brit. J. Pharmacol.* 1956, **11**, 394.
3. Falkner Hill, E. *Brit. J. Anæsth.* 1957, **29**, 12.

MEDICAL STUDENTS LOOK WEST

SIR,—The opinions of Mr. Cohen and his fellow students (Aug. 31) about the examination system for the M.D. degree in American universities reminded me of an interesting day spent shortly before the war as a coöpted examiner in a well-known medical school in the United States. The clinical part of the final examination in medicine consisted of a viva voce and an examination of one patient—what in English parlance would be called a "long case." In the viva I asked the candidate I was examining how he would differentiate chickenpox from smallpox. Even with prompting it was quite evident that he had no ideas on the subject, and one of my fellow examiners said that it was a long time since the candidate had taken his fever course, and suggested that we should pass to other subjects. The candidate was then sent to another room to examine his long case.

After some twenty minutes we went in. The patient was middle-aged, extremely emaciated, and deathly white. When his abdomen was uncovered it was easy to see a large swelling in the epigastrium, which moved with respiration. Palpation confirmed the presence of an extremely large, hard, and irregular liver, almost certainly secondary carcinoma. I asked the candidate whether he had made any diagnosis. He gave us an adequate disquisition on Castle's intrinsic factor and maturation of red cells and rather diffidently made a diagnosis of pernicious anæmia. Although he had felt the large liver it did not seem to him to have any special significance and he suggested cirrhosis as a possible explanation.

The sequel was interesting. An examiners' meeting was held in the afternoon. All the teachers in the medical school were there—about forty including myself. When the candidate whose examination I have described came up for consideration there was a long discussion as to whether he should be awarded the M.D. with honours or merely the M.D. The candidate in question had already been appointed to a teaching post in the department of physiology in another university and was expected to achieve fame as a physiologist. About half the examiners took the view that the university would stultify itself by not giving him the M.D. with honours. Others maintained that the M.D. was an indication of ability in medicine and not in physiology. Eventually a vote was taken and by a small majority it was decided to give the M.D. without honours. The difference between final examinations in the United Kingdom and the United States is well exemplified by the fact that no-one even suggested that the candidate should be failed.

London, S.E.1. J. J. CONYBEARE.

SIR,—In view of the correspondence regarding our article, we should like to restate our impression of American and British outpatient teaching in what may be a clearer fashion.

The American methods of outpatient teaching which we described are those used in general medical clinics; these have been deliberately reconstituted in many American teaching hospitals and it is in them that most of the outpatient teaching is done. In this country a substantial amount of teaching is done in specialist clinics as well as in the general ones.

It is the common purpose of the American and British systems to give the student an idea of the problems arising

in outpatient practice and to provide further experience in clinical method. But there are outstanding contrasts in the remaining objectives of the two systems. The traditional British system attempts to teach medicine mostly by a demonstrative method and to teach the student, in Sir Charles Symonds's words, "flexibility and speed in outpatient practice . . . how to work efficiently against the clock." The specialist clinics are, perhaps, especially suited to these objects. The American system seeks to provide a measure of responsible experience in understanding and dealing with a patient's problems, and also to give the student a better acquaintance with the doctor-patient relationship and with the idea of the patient as a whole person.

Thus, the *objects* of the two systems are to a great extent different. It follows that the *methods* employed to attain these objects cannot be compared on a "better-or-worse" basis. In fact, the objects are complementary rather than mutually exclusive. Both methods are valuable and we feel that both should be provided, if possible.

We are, of course, not competent to judge the methods used to achieve educational objectives. We would, however, like to mention the answer given to us by many Americans when we asked how a student trained in outpatient medicine under their system could be expected to cope on qualification with a busy outpatient practice. The gist of their replies was that after qualification the doctor has at least one or two years' further training before this difficulty arises, in which time he will have substantially improved his clinical method; he will then know by experience what questions to ask and what systems to examine in a particular outpatient. They did not feel that it was the best thing in the long run to encourage students to develop this important technique from the outset. Rather it was better for the student to develop his own clinical method at his own pace, to spend time in getting to know the patient as a whole and in developing a good relationship between himself and his patient.

R. D. COHEN
DAVID T. HUGHES
PETER RICHARDSON.

The London Hospital Medical College, London, E.1.

PLACEBOS AND PLACEBOS

SIR,—What follows is a suggested double-placebo method for reducing side-effects encountered with such drugs as tranquillisers.

We have strong evidence to indicate that the incidence of side-effects in using any preparation (active drugs as well as placebos) is particularly great among the patients in whom the symptomatology has a strong emotional overlay. Thus, placebo effects can be expected to comprise a substantial proportion of side-effects encountered in the use of many active drugs.

In order that the physician may be able to (1) identify and differentiate side-effects associated with placebo response from those associated with pharmacological action of the drug used, and (2) reduce or eliminate placebo effects which interfere with the effectiveness of active drugs, I should like to suggest the following double-placebo technique:

(1) We prepare two types of placebo: (*a*) a horrible-looking rather spectacular placebo, and (*b*) a placebo identical in appearance with the active drug.

(2) Before dosing with the active drug, the physician prescribes the horrible placebo.

(3) If he gets side-effects with the horrible placebo he tells the patient that he is now going to replace it with something which will do the same job, but without nausea or what have you. This replacement, of course, is the second placebo.

(4) If the second placebo does eliminate the side-effects encountered with the horrible placebo, then our aim has been accomplished to its fullest degree, and the patient is put on the real drug.

(5) If the second placebo fails to eliminate the side-effects from the horrible placebo, or stimulates its own set of effects, at least the physician will be able to recognise their source when he puts the patient on the pharmacologically active drug.

CONRAD CHYATTE.

De Paul University, Chicago.

CORK-RETAINER FOR TRANSFUSION SET

SIR,—I have only just seen Dr Bishop's lucid description (June 8) of his cork-retainer for the M.R.C. transfusion set. We have been using an almost identical model at the London Chest Hospital since 1954 for a prototype pressure set, which was made for us by A. L. Hawkins Ltd., of London.

When changing bottles during transfusion it is important to screw the cap into light contact only with the cork, otherwise frequent compression fractures of the air tube against the bottom of the bottle result, or else the cork is difficult to remove. Either occurrence could be tedious during an emergency.

R. N. G. ATHERSTONE.

The London Chest Hospital, London, E.2.

GASTROJEJUNAL INTUSSUSCEPTION DUE TO BENIGN GASTRIC LEIOMYOMA

SIR,—A little over 1% of all gastric neoplasms are benign [1 2]; and in a series of 931 benign gastric tumours, 36·6% were leiomyomata.[3] Maingot [4] states that leiomyomata rank third in importance among the growths of the stomach.

These tumours may lead to ulceration, hæmorrhage, or pyloric obstruction, but only one previous report [5] can be found of intussusception, which complicated the case recorded here.

An Arab woman, aged about 30, had first had upper abdominal pain during Ramadhan when she was two months pregnant. After a short period of observation the pain disappeared.

Seven months later, after her confinement, severe upper abdominal pain developed and a mobile mass was palpable at the umbilicus. Round-worm ova were present in the stools, so a vermifuge was given followed by an enema. A very large quantity of worms was passed, the abdominal mass disappeared, and her obstructive symptoms were relieved. She was very anæmic so a blood-transfusion was given and she was discharged well.

She had had two further attacks of pain, during one of which her family subjected her to the traditional remedy of branding with a hot iron, and last January (10 months after the first attack) she was admitted with abdominal pain. She was emaciated and apyrexial. No abdominal mass was present. Iron was given by mouth and by injection, since her hæmoglobin level was 26%. A week after admission, the pain began to increase. The hæmoglobin was 59% and stools contained no amœbæ or ova.

Two days later the pain suddenly became much worse, and a mass was palpable in the epigastrium, about 3 in. in diameter, soft, tender, and mobile. The rectum was empty and there was no blood on the examining finger. The hæmoglobin was 38%.

In view of the history a vermifuge was given though no ova had been found; but no worms were produced. The mass became sausage-shaped and very tender, and extended to the left of the umbilicus. Next morning the mass was smaller, less tender, and more mobile. That night the patient vomited 2 pints of altered blood.

Donors of the correct group had by then been obtained, and the patient was taken to the operating-theatre, but collapsed suddenly and became almost pulseless. 2 pints of blood was given under pressure; she was returned to the ward and the transfusion continued with dextran.

Next morning her hæmoglobin was 55%; operation was undertaken as a desperate measure. Her abdomen was now rigid and resistant.

Operation.—The duodenum and upper jejunum were red and grossly distended by a sausage-shaped tumour which

1. Aird, I. A Companion in Surgical Studies. Edinburgh, 1957.
2. Eusterman, G. B., Senty, E. B. *Surg. Gynec. Obstet.* 1922, 34, 5.
3. Minnes, J. F., Geschickter, C. F. *Amer. J. Cancer*, 1936, 28, 136.
4. Maingot, R. Abdominal Operations. New York, 1948.
5. Eliason, E. L., Wright, V. W. M. *Surg. Gynec. Obstet.* 1925, 41, 461.

could not be reduced by external manipulation of the gut. An opening was made into the jejunum over the apex of the tumour, which was found to consist of a smooth pedunculated mass, about 2 in. in diameter, arising from the middle of the lesser curve, which had drawn down the whole of the stomach with it. The intussusception was gently reduced through the œdematous pylorus. The base of the tumour was soft and free from infiltration. The stomach was opened and the tumour-bearing area of the wall excised. Since the œdema at the pylorus might cause further obstruction, a retro-colic gastro-jejunostomy was made.

Histological examination showed that the tumour was a benign leiomyoma.

Progress.—Convalescence was complicated on the second day by a pneumonia which responded to penicillin. She was discharged well on the ninth postoperative day.

There is an association between chronic gastritis and benign neoplasm.[4] This patient's symptoms began during Ramadhan when the daylight fast and large meals at night lead to digestive troubles. The intussusception had obviously reduced itself several times giving rise to the confusing changes in physical signs.

My sincere thanks are due to Dr. Jean Infield for her help in reviewing the literature.

Government Hospital, Bahrain. BETTY M. L. UNDERHILL.

ACNE VULGARIS

SIR,—I was very interested to read Dr. MacKenna's letter last week on acne vulgaris and its treatment with a gonadotrophic preparation. I have been using a similar dose and my immediate results resemble his. There is very good improvement in about 60% of patients. It is too early yet to know how many of them will relapse.

London, W.1. E. LIPMAN COHEN.

INFUSION NEEDLES

SIR,—The correspondence [6 7] concerning infusion needles has only now come to my notice. I should like to draw attention to my description of a suitable needle for this purpose.[8] It is manufactured by Willen Bros., 44, New Cavendish Street, London, W.1.

Thomayer Hospital, Prague. J. H. WAELSCH.

MANAGEMENT OF ANASTOMOTIC ULCER

SIR,—I was interested to read the article by Dr. Balint and his colleagues in your issue of Sept. 21. I note, in their summary, that "For anastomotic ulcer following partial gastrectomy, abdominal vagotomy, with or without revision of the anastomosis, or, if necessary, a limited gastric resection to remove the ulcer, is recommended."

I can record only seven patients with anastomotic ulceration following gastrectomy which I have treated by abdominal vagotomy. One of these patients has been followed for 9 years, one for 7 years, three for 6 years, and one for 2 years. Each one of these patients has remained well and they have all had a chronic anastomotic ulcer, sometimes with an enormous crater. The remarkable thing has been the speed of healing after vagotomy for careful radiological studies, showing mucosal pattern, have demonstrated healing of an enormous ulcer as early as 8 days and, as I have said, this healing has been, in each case, maintained.

The point I wish to make here is that the proper treatment of anastomotic ulceration after gastrectomy, even if the gastrectomy is not a high one, is, in my view, complete abdominal vagotomy without further gastric surgery, which must, even in experienced hands, carry some risk of morbidity and, in less experienced hands, mortality. The surgeon has no method of deciding at operation which cases may or may not need gastric surgery as well as vagotomy and, therefore, he should use vagotomy and await the result.

I suspect that, if vagal-nerve section can be made complete (and we now have a means of proving it before the abdomen is shut), there will seldom be need for further gastric surgery, no matter how large or how chronic the ulcer may be.

London, N.W.1. HAROLD BURGE.

POLYTHENE GIVING-SETS FOR TRANSFUSION

SIR,—I wholeheartedly agree with Dr. Cook (Aug. 10). For the past nine months I have been working up in the Arctic and have found the 'Polythene' giving-sets most useful, since not only are they easier to put up compared to the ones I used while doing hospital work in Manchester, but they are also "disposable." They are easy to carry, and pack into very little space. This is a great advantage to me, because I travel around my practice of several hundred square miles by plane, helicopter, snow-mobile, or dog-team sleds. I can put up a drip in an old Eskimo shack just as easily as in my base hospital.

Somewhere in the Arctic. R. R. THOMAS.

BONE-MARROW FOR TREATMENT OF LEUKÆMIA

SIR,—We were glad to learn that you have drawn attention to the extremely interesting recent developments in bone-marrow transplantation. But we were somewhat disappointed to find that your leader (July 20) suffers from several misinterpretations, omissions, and errors.

It is certainly an omission that no reference has been made to the work of Hollcroft et al.[1] These investigators introduced the method of total-body irradiation with lethal X-ray doses followed by bone-marrow injections for the treatment of experimental leukæmia in guineapigs.

Both the papers of Jacobson et al.[2] and Cole et al.,[3] referred to in the first section of your article, deal with irradiated *mice*, not rats.

Proof that the transplanted marrow-cells proliferate in the irradiated hosts' tissues came simultaneously (March, 1956) from three different laboratories.[4–6] In all, *four* different methods were used.

In discussing the experiments of Nowell et al.,[5] you say: "After twenty-one days deaths began to occur from the odd reaction previously noted, but in those animals that survived beyond thirty days the phosphatase-positive rat cells were being replaced by phosphatase-negative cells that were presumably from the mouse's own recovering tissues." But Nowell et al.'s paper contains only the following statements concerning this particular aspect:

(*a*) "Data beyond those at 4 weeks are, at present, extremely limited because of the continuing deaths in the heterologous group. However, a few mice from previous experiments have survived beyond the 2d month, and, in those examined, phosphatase-positive cells were found in blood smears up to 16 months after irradiation and injections of rat marrow."

(*b*) "Since this paper was originally submitted for publication, additional mice have survived beyond 30 days after X-irradiation and treatment with rat bone marrow. A number of these have shown on examination, a transition from phosphatase-positive to phosphatase-negative leukocytes in blood and bone marrow smears, suggesting that the heterologous bone marrow has been replaced by cells of mouse origin."

Similar data have been provided by van Bekkum et al.[7]

6. Furniss, D. *Lancet*, 1957, i, 739.
7. Thorne, N. A. *Ibid*, p. 888.
8. Waelsch, J. H. *Brit. med. J.* 1948, i, 897.

1. Hollcroft, J., Lorenz, E., Congdon, C. C., Jacobson, L. O. *Rev. mex. Radiol.* 1953, 7, 115.
2. Jacobson, L. O., Simmons, E. L., Marks, E. K., Elbridge, J. *Science*, 1951, 113, 510.
3. Cole, L. J., Habermeijer, J. G., Bond, V. P. *J. nat. Cancer Inst.* 1955, 16, 1.
4. Ford, C. E., Hamerton, J. L., Barnes, D. W. H., Loutit, J. F. *Nature, Lond.* 1956, 177, 452.
5. Nowell, P. C., Cole, L. J., Habermeijer, J. G., Roan, P. L. *Cancer Res.* 1956, 16, 258.
6. Vos, O., Davids, J. A. G., Weyzen, W. W. H., Bekkum, D. W. van. *Acta physiol. pharm. neerl.* 1956, 4, 482.
7. Bekkum, D. W. van, Vos, O., Weyzen, W. W. H. *Rev. Hémat.* 1956, 11, 477.

Therefore loss of the grafted cells in the thirty-day survivors is certainly not the rule and occurs only in a small percentage of the animals.

The American journal, *Blood*, recently published a similarly unsatisfactory editorial on the same subject, but it was much more of a shock to us that you, Sir—editor of a journal of British and *foreign* medicine, &c.—had apparently not even consulted one of the specialists on bone-marrow transplantation in your own country.

Especially for the purpose of "pooling the experience of several laboratories," a meeting was held in Gatlinburg, U.S.A., in April this year. It has surprised us that none of the 5 or 6 British scientists attending has so far protested against your inadequate presentation of these extremely interesting advances.

Medical Biological Laboratory, National Defense Research Council T.N.O., Rijswijk Z.H., Netherlands. D. W. VAN BEKKUM J. A. COHEN.

*** We were at fault in saying that the work of Jacobson et al. and Cole et al. was done on rats. Our reading of the report by Nowell et al. differs only in emphasis from that by Dr. van Bekkum and Professor Cohen: the important feature is that transition from phosphatase-positive to phosphatase-negative cells was found. In reproaching us for failing to mention the paper by Hollcroft et al. in *Revista mexicana de radiologia*, and all four methods for studying transplanted marrow-cells, our correspondents seem to imply that, whenever we discuss a subject, we should be comprehensive and refer to all relevant papers and work. But our leaders are not intended to be complete review articles such as may be found elsewhere: our purpose is rather to comment, comparatively briefly, on new findings and trends. We hope that the references we supply will suffice to guide interested readers to accounts that do not receive specific mention.—ED. L.

Public Health

Influenza

MANY new outbreaks of influenza have been reported in the North of England, the Midlands, and South Wales; elsewhere most outbreaks have been in such semi-closed communities as Service units, holiday camps, and schools. Many general practitioners have never been so busy; one reported that every patient at his surgery had influenza—two-thirds of them with temperatures over 100°F. Some waiting-rooms are so overcrowded that patients wait in the rain. In most cases the disease is mild, with recovery in four days; but there have been a few deaths in all age-groups. There were 12 deaths in Manchester in the week ended last Monday,[1] and 25 were reported in the whole country on that day. The number of deaths at present is very small compared with the number of cases, and appears, for example, to be much below the death-rate recorded in Indonesia. In several British centres the virus has been identified as influenza A, which includes the Asian virus, but the World Influenza Centre has not yet identified it definitely as the Asian type.

Illness among the staff has affected many hospitals; some have forbidden visiting, and others have restricted or even suspended admission and outpatient services. The Ministry of Health said on Saturday that distribution of influenza vaccine under the priority scheme for the inoculation of hospital and family doctors would begin late this month or early next month. The medical department of the Admiralty has asked the Ministry of Health for vaccine for the inoculation of younger ratings. Influenza has been widespread in ships and shore establishments, and a submarine has been withdrawn in consequence from a NATO exercise.

Other areas where influenza is increasing include West Africa and South America; the spread there is faster than in Europe and North America. The pandemic is declining in Asia and East and South Africa.

1. *Times*, Sept. 24.

In a letter on p. 639 Professor Macleod expresses concern lest the threat of a severe pandemic (perhaps in the form of a second wave) be underestimated, and he gives his reasons for believing that *Hæmophilus influenzæ* may be associated with certain types of influenza of high mortality.

Poliomyelitis

Uncorrected poliomyelitis notifications in the week ending Sept. 14 (37th week of the year) were as follows (previous week in parentheses): paralytic 116 (158), non-paralytic 84 (121); total 200 (279). The following figures compare this year, up to and including the 37th week, with the preceding nine years.

Year	Total cases up to and including 37th week	Cases in 37th week
1948	1288	74
1949	2987	342
1950	5604	478
1951	2013	90
1952	2974	183
1953	3705	227
1954	1574	92
1955	3857	411
1956	2297	112
1957	4313	200

Eradication of Tuberculosis in Cattle

Tuberculosis has been cleared from all herds in four areas of Great Britain, each comprising several counties, that were declared eradication areas in March; two are in England, one in Wales, and one in Scotland. Cattle in these areas not previously attested (about 1% of the total) were tuberculin-tested, and those with positive reactions were slaughtered. The four areas will be declared attested on Oct. 1; by then nearly 3,000,000 cattle—over a quarter of the total in Great Britain—will be in attested areas. 4,500,000 more are in areas expected to be attested in the next two years.

Diary of the Week

SEPT. 29 TO OCT. 5

Tuesday, 1st

UNIVERSITY OF LONDON
5.30 P.M. (Westminster Medical School, Horseferry Road, S.W.1.) Prof. E. M. Papper (Columbia University): Circulatory Complications of Improper Respiration During General Anæsthesia.

UNIVERSITY COLLEGE, London, Gower Street, W.C.1
5 P.M. Prof. M. Heidelberger (Rutgers University): Chemistry of Proteins and Carbohydrates in relation to Immunological Specificity.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. G. C. Knight: Intracranial Abscess.

Wednesday, 2nd

ROYAL SOCIETY OF MEDICINE, 1 Wimpole Street, W.1
5.15 P.M. *History of Medicine.* Mr. Terence Cawthorne: Julius Cæsar and the Falling Sickness.
8 P.M. *Surgery.* Mr. Norman Tanner, Mr. R. H. Franklin, Mr. Vernon Thompson, Mr. Donald Barlow: Hiatus Hernia.

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
2 P.M. Prof. N. F. Maclagan: The Place of Chemical Pathology in Medicine.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. W. Riddell: Rôle of Fungi in Dermatology.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, London, S.W.3
5 P.M. Mr. Norman Barrett: Pulmonary Hydatid Disease.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, Gray's Inn Road, W.C.1
5.30 P.M. Dr. H. Haber: Precancerous Conditions of Skin and Mucous Membrane.

BIRMINGHAM MEDICAL INSTITUTE, 36 Harborne Road, Edgbaston, Birmingham, 15
8.15 P.M. *Midland Medical Society.* Mr. Ian Fraser: A Recent Medical Visit to Soviet Russia.

Thursday, 3rd

ROYAL SOCIETY OF MEDICINE
5 P.M. *United Services.* Wing-Commander P. F. King and Flight-Lieutenant P. Gannon: Problem of Noise in The Royal Air Force.
8 P.M. *Neurology.* Dr. W. Ritchie Russell: Physiology of Memory. (Presidential address.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Prof. E. Kerpel-Frondius (University of Pecs): Metabolic Aspects of Infantile Malnutrition.

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Dr. J. Risser: Concepts of Scoliosis.

Friday, 4th

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S.E.5
4.30 P.M. Sir Cecil Wakeley: Some Aspects of External Herniæ. (Thomas Percy Legg lecture.)

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. H. H. G. Eastcott: Second Thoughts on Arterial Reconstruction.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P.M. Dr. C. H. Edwards: Neuralgias and Headaches.

Obituary

HUGH MacLEAN

M.D. Aberd., D.Sc. Lond., M.Sc. Lpool, F.R.C.P.

IT is over twenty years since Professor MacLean was forced by ill health to resign his chair at St. Thomas's Hospital, and today too few may recall how much he contributed to chemical pathology. One measure of the value of his work, however, is that the methods which he introduced in the study of diabetes and of renal disease are still in general use.

He was born in 1879, and he studied medicine at the University of Aberdeen, graduating M.B. in 1903 and taking his M.D. with the highest honours the following year. One of his teachers, Prof. J. A. MacWilliam, was a collaborator of Sir James Mackenzie, and under his influence MacLean was early taught to interpret disease in terms of impaired efficiency and to study the application of the principles of physiology to medicine. From a lectureship in the department of physiology in the University of Aberdeen he went to the department of physiology in the University of Liverpool, and in 1910 he came to London as senior assistant in the biochemical department of the Lister Institute. There, with the late Ida Smedley, whom he married in 1913, his work on the lecithins was begun. These investigations were later published as his classical monograph *Lecithins and Allied Substances* (1918). He was also appointed to the staff of St. Thomas's Hospital as chemical pathologist. During the 1914–18 war much of his work on kidney function was done, and with Professor de Wesselow at Étaples he investigated the value of renal tests. In 1919 his report on war nephritis was published by the Medical Research Council. His knowledge of these problems led to his appointment as consulting physician to the Ministry of Pensions.

After the war he returned to St. Thomas's, at first to his old appointment of chemical pathologist. His publications at this time included an account of his method for estimating blood-sugar, and he also delivered at the hospital a memorable series of lectures on applied physiology. These lectures may have been one of the reasons for his appointment in 1920 as professor of medicine and director of the medical unit. A student and hospital resident of those years writes:

> MacLean's appointment was the result of bold decisions made by other people (the hospital governors, no doubt advised by the medical staff) to create a "medical unit" and to appoint someone from foreign parts (with an outlook very foreign to the somewhat stuffy native view), and it appeared to us that MacLean was himself the embodiment of the "new look," the medicine of the test-tube. The hospital staff was not without its characters, but this was something "rare and strange." He carried with him an aura of change—change in the convention of teaching and of attitude to patients, and it was symptomatic (and perhaps an indication of unusual insight by the matron of that time, Miss Lloyd-Still) that his ward sister should be herself a woman of unusual independence, unconventional to a degree which put her thirty years ahead of her time in establishing regular evening ward visiting by the wives and mothers of her patients.
>
> MacLean, although not an exceptionally big man, gave the impression of being massive. His broad Aberdeen accent was a source of great joy to us. He was not an outstanding clinician, but a better one than some of his critics suggested. He had considerable stature as a "scientific physician," which is by no means to say that he was lacking in human sympathy. If he was not a great man, he was certainly an outstanding one.

Thanks to MacLean's personal qualities the appointment was a success and he contributed a great deal to the post-war reconstruction of the medical school. He was largely instrumental in obtaining for the hospital the generous endowment which made possible the Dunn Laboratory. In 1924 during a visit to the United States he won the interest and support of the Rockefeller Foundation, which gave £15,000 towards the unit building.

As a teacher MacLean was also invaluable to the hospital. His work attracted to the wards an enormous number of diabetics and nephritics, which gave an opportunity to the student of those days to see material which is probably now unobtainable. He was greatly interested in postgraduate teaching—a postgraduate round which he started had to be discontinued because too many people attended it—and he encouraged the development of the clinic system.

Outside the hospital he gave in 1926 the Oliver-Sharpey lectures at the Royal College of Physicians of London on carbohydrate metabolism, and the following year he was elected F.R.C.P. He edited a series of monographs on *Modern Methods in Diagnosis and Treatment* to which he himself contributed the three volumes on renal diseases, glycosuria and diabetes, and digestion and gastric disease. For many years he had been carrying a heavy load of work and responsibility, and a breakdown led to his premature retirement in 1936. He died on Sept. 18 at the age of 78. He leaves a son and a daughter.

G. F., who knew Hugh MacLean during his years as professor of medicine, writes:

> I always remember his kindness and encouragement to a comparative stranger at first, and a junior, and how appreciative he always was for anything one could do for him. In his results and publications he was meticulous in his acknowledgement of one's small efforts to help. He had few outside interests, but his main hobby was shooting, and on several occasions I X-rayed his gun barrels to see if we could determine anything of their structure. He was a great reader and I was often able to get help from him over the selection of textbooks on my subject. I have always retained a feeling of gratitude and admiration for a great and kindly man of simple mind.

R. J. V. P., another colleague of these earlier years, describes Hugh MacLean as:

> a man not easily forgotten by those who were taught by him or worked under him. A tall, stoutly built Scot, he always carried with him to the wards and laboratory something of the slow deliberate thoroughness which he inherited from the lonely Highlands in which he spent his youth. He used to say that the proper way to teach was to tell students what you were going to say, to say it, and then to tell them what you said: he certainly followed his own advice, and no-one was ever left in any doubt as to his views on any scientific matter. Despite his distinction he always seemed a little remote from the traditions of London consultant medicine, and although his services in reopening medical education at St. Thomas's after the war were of the highest standard, he had few intimate friends among his colleagues, and perhaps not all of them realised that he was among the few contemporary names destined long to outlive their office.

DAVID TURNBULL RICHARDSON

C.B., M.C., M.B. Edin., D.P.H.

Major-General Richardson, who was director of hygiene at the War Office from 1941 until his retirement from the Army in 1945, died on Sept. 14 at Badachro, Ross-shire, at the age of 70.

Born at North Berwick, he graduated in medicine from the University of Edinburgh in 1910 and was commissioned as lieutenant R.A.M.C. in 1912. After joining for duty in Edinburgh he went in 1914 to India and after service in Jubbulpore and Colaba he was posted for duty with the Aden Field Force. He was awarded the M.C. in 1918. Returning to the United Kingdom in 1920 he served in Scotland and in Ireland. After a course at the Royal Army Medical College, he qualified with distinction as a specialist in hygiene. His work in Glasgow in 1923 under Prof. E. P. Cathcart, F.R.S., led, on his return to India, to special duty with Colonel William Campbell on the energy expenditure of the British and Indian soldier. In 1928 he was appointed assistant professor of hygiene at the Royal Army Medical

College, and, after further service in Jamaica and at the War Office as assistant director of hygiene, he was appointed professor of hygiene at the college in 1938. In the late war he served in France as deputy director of hygiene G.H.Q., B.E.F., and as D.D.M.S. 6th Corps in Northern Ireland before becoming director of hygiene at the War Office with the rank of major-general in 1941. He was appointed honorary surgeon to the King in the same year and C.B. in 1945. He was also a commander of the Order of St. Olav.

Of these last strenuous years A. E. C. writes:

Duty at the War Office from 1941 to 1945 called for all the resources of a direct and forthright character. The inevitable work at desk and in committee was at times a sore trial to Richardson, but his tenacity of purpose was well shown in his work for the supply of pyrethrum and the introduction of D.D.T. for Service use. His record of service indicates but little of his widespread interests and influence. Shortly before his retirement he wrote, for War Office circulation, a paper entitled A New Life for the Soldier which was not only visionary but summarised his work and aspirations in Army health and hygiene. Much of what he wrote may now appear superfluous, but was at that time a stimulus and challenge to his successors and to Army administration in improving the lot of the soldier.

David Richardson was never all things to all men. He had his prejudices as those who worked with him well know, but all had no doubt as to where he stood on any subject. In his official record of service there is a small note "can sketch." Few would have recognised in him the creator of "Noffy," the anopheles heroine (or villainess) of a cartoon series on the prevention of malaria. More of his acquaintances would have realised his love of history and the Highlands and may not have been surprised when on retirement he settled near Gairloch in Wester Ross. Many of his friends prophesied, and all hoped, that he would at some time return to be for a while among those with whom he had served, but only thrice did he go far from his delightfully situated house, his sea-fishing, and gardening. He said he would retire and he did—to the great benefit of the many crofters and others whom he helped in the locality where he settled—not to mention the visitors whom he delighted to entertain.

J. W. H., who was one of his temporary civilian colleagues, affectionately recalls Richardson's half simulated doubt about efforts to keep up the professional morale of serving medical officers by publishing what were meant to be helpful annotations on matters of topical interest.

"If you want these fellows to carry out a certain treatment, why don't you issue a firm order?" Despite this line of argument, which he often pressed, he realised well enough the point of what was being attempted and he was often far more helpful with private and personal suggestions than he would have wished it to be generally supposed that he would be. Not all of his suggestions were perhaps meant to be taken seriously—for example, that medical officers should be invited to engage in an inquiry to test his often expressed belief that the best preventive measure against the common cold was the regular taking of snuff.

My last memory of him covers the evening before he set out from Millbank to leave the Army for civilian life. I had some fear that these hours would be a sad occasion; but this was not so. No temporary officer heading for a renewal of the joys of family life could have beaten David Richardson's happy anticipation of the move he was about to make. He sat there telling us eagerly about the house in the Western Highlands which was to be his new home. Obviously the picture of it had been in his heart and mind on many hot and dusty occasions in his years of service. This house was clearly an ideal place—hard to reach by road but of easy access by boat across the loch. That would ensure that only the right kind of company came to share the joys of fishing, general handiwork, and hospitality which were to be the main things of his new life. Unquestionably he must have felt some emotion at leaving the Army: it had been his life for so many years and he had served it with enthusiasm and courage; but here was a new life ahead and the time to walk out of uniform and into fishing boots could not come quickly enough. Whatever his qualms, he hid them from us by the youthful way in which he reached out to the new phase of his life. Many who knew him for only a few years of the war, but who remember him with the affection due to all resolute characters, will hope that his idyll came true and will wish only that it could have been longer.

L. T. P., a colleague of long standing, writes:

David Richardson was a Scot and loved everything connected with his native land. Dressed in his kilt his magnificent figure with massive shoulders made his appearance outstanding. He had a wide knowledge of country life and was always entertaining when recounting his experiences. He was a delightful companion—openhearted and generous. A thoughtful gesture was when he presented the headquarters mess of the American Army Medical Corps with an old-fashioned Scottish snuff box of the finest Highland craftsmanship as a symbol of Scottish friendship.

In the realm of sport he excelled in the Royal and Ancient game, having spent his boyhood within easy reach of one of the finest seaside golf courses in Scotland. He was an expert yachtsman and a keen shot and deer-stalker. With so many interests in sport it was natural that his kit would be extensive, and to move it around, together with his family, he acquired a large-capacity car. When ordered to India he resolved to sell this car. But many years ago, it may be recalled, the market for such a car was limited and no-one would bid him more than a few pounds for it. So he decided the best thing to do was to load the car with all his belongings, drive it to the docks, and abandon it on the quayside. This he did and the car incident, as far as he was concerned, was closed. But a year or so later to his surprise he received a fat cheque from the police with a polite note to say that as he had not claimed his car it had been sold by auction. Before his care-free, enthusiastic attitude to life his energetic ability, and his charm of manner difficulties melted away. But it was the deep sincerity which lay behind his broad smile that endeared him to all who knew him.

JAMES MACKINNON

D.S.O., M.B. Glasg.

Dr. Mackinnon died at the age of 81 on Sept. 8 at his home in Sheffield, where he had practised for over fifty years. He qualified from the University of Glasgow in 1900, and after holding house-appointments at the Victoria Infirmary in Glasgow and at the Leith Fever Hospital, he came to Sheffield in 1903. He joined the late Dr. Longbottom in the Pitsmoor district of the city, first as an assistant, then as partner, and finally he succeeded to the practice. From 1924 to 1948 he was chairman of the local medical and panel committee, and from 1939 to 1952 of the National Service medical board.

During the 1914–18 war he served in France and was in command of a field ambulance. The unit included a field hospital for the treatment of scabies. Lieut.-Colonel Mackinnon devised an incinerator which, in disposing of solid and fluid excreta, generated sufficient heat to boil water for baths and dry clothes. He was awarded the D.S.O. in 1917. The following year he became A.D.M.S. of the 66th division. After the war an Old Comrades Association was formed in Sheffield in connection with the local Territorial medical units, with Dr. Mackinnon as president. He was also president of the Caledonian Society of Sheffield.

E. F. F. writes:

James Mackinnon's personality and tall handsome appearance made him an outstanding figure in any company. He was usually the leader of any medical deputation that interviewed the local authority. He put forward the medical point of view with moderation and effect, for he had vision for the future, tolerance for another man's views, and ability to convince others of the wisdom of his advice. He was the main inspiration of the Pitsmoor Medical Guild which has played an important part in maintaining amicable professional relationships. He was always keen on games and played to win. He was the originator of the Sheffield medical golfing society and its president for eighteen years. He was skip of the rink of the Sheffield curling club, which takes part in national competitions. In his younger days he was a keen tennis-player. He was a wonderful companion as a host, on a golf course, or at the fireside. His patients recognised and valued his clinical acumen, but prized still more his friendship. They placed implicit trust in his opinion and advice not merely on medical matters, but also in many of their social and economic perplexities.

VERA NORRIS

M.B. St. And., Ph.D. Birm.

Dr. Norris was lecturer on medical statistics at the Institute of Psychiatry in London till she moved to Inverness last year, when she became regional statistical medical officer to the Northern Regional Hospital Board.

She graduated M.B. from the University of St. Andrews in 1944 and later held house-appointments at Dundee Royal Infirmary. After two years' service with the Indian Medical Service she returned to this country to work with a Halley Stewart research fellowship in Professor Hogben's department in the University of Birmingham. In 1949 she was appointed senior statistical officer to the Birmingham Regional Hospital Board and lecturer in medical statistics to the university. Two years later she gained the appointment at the Institute of Psychiatry. She moved to Scotland last year when her husband, Dr. Donald Mackay, was appointed to a hospital in Inverness.

A. L. writes:

Vera Norris's work since the war had won her an outstanding place as a medical statistician, specially concerned with the complex problems of mental illness. Trained in a rigorous school, she brought clear thought and technical competence to bear on the analysis of tangled data; it was, however, in her grasp of the implications of her work that her exceptional ability became evident. She looked at statistical data dispassionately, but with a full awareness of how they could be used to bring about medical and social betterment. From her earlier studies on regional hospital planning and the health of the school-child to her last major undertaking—an exhaustive inquiry into the course of mental illness—this controlled determination to use vital statistics for improving social action and clinical practice was plainly manifest. The monograph containing the results of her last investigation, which had occupied her for five years, is due to appear very shortly: it is sad that she did not live to see it published. With remarkable courage she had lately undertaken fresh duties in Scotland, and was planning detailed studies even during her final illness. Unlike the conventional idea of the statistician, aridly detached from the business of life, she was always mindful of the people who lay behind the statistics, and of their needs. The same generous spirit informed her personal life: warm-hearted, open and direct in all her dealings, she was rich in friendships.

Births, Marriages, and Deaths

DEATHS

MAXWELL.—On Sept. 9, in a road accident at Eaton Socon on the Great North Road, John Smart Maxwell, M.B., F.R.C.S.E., of 46, North Bar Without, Beverley.

Appointments

CRAIG, ALEXANDER, M.B. Edin., D.P.M.: consultant psychiatrist, North Wales Hospital, Denbigh.

DAVIDSON, R. C., M.R.C.S., D.A.: assistant anæsthetist, Barnsley hospitals.

LORIMER, A. H., M.B. Aberd., DIP.PSYCH.: psychiatrist (S.H.M.O.), Bangour Village Hospital, Broxburn, West Lothian.

MCCAREY, A. G., M.D., B.SC. Glasg., D.M.R.D., D.R.: honorary assistant consultant radiologist, Providence Hospital, St. Helens.

PATTERSON, T. J. S., M.B. Camb., F.R.C.S.: consultant plastic surgeon, United Oxford Hospitals and the Oxford Regional Hospital Board.

STEWART, A. M., M.B. Edin., F.R.C.S.E., D.M.R.D.: consultant radiologist, North-eastern Regional Hospital Board, Scotland.

East Anglian Regional Hospital Board:

KIRK, A. G., M.R.C.S.: registrar in psychiatry, St. Andrew's Hospital, Norwich.

LINTON, C. D., M.B. Brist., D.OBST., D.A.: senior anæsthetic registrar, Norfolk and Norwich area hospitals.

MELLON, E. R. F., M.D. Dubl., D.P.H., D.P.M.: consultant psychiatrist, St. Andrew's Hospital, Norwich.

TWEED, W. M. E., M.B. Lond., D.OBST.: registrar in obstetrics and gynæcology, East Suffolk and Ipswich hospital group.

Colonial Appointments:

CHEN, J. H. M., M.B. Hong-Kong, F.R.C.S.: senior specialist, Nigeria.

CLARKE, G. H. V., M.B. Lond.: senior specialist, Nigeria.

LOW, A. D., M.R.C.S.: senior M.O., St. Vincent, Windward Islands.

MCADAM, I. W. J., M.B. Edin., F.R.C.S.: senior specialist, Uganda.

MCKNIGHT, A. L., M.B. Leeds: senior M.O. (clinical), Southern Cameroons.

MOODIE, A. S., M.B. Glasg., D.P.H.: senior specialist (tuberculosis service), Hong-Kong.

PAYNE, R. F., M.R.C.S., D.T.M. & H.: medical superintendent, Victoria Hospital, Gambia.

Notes and News

OVERTIME IN MENTAL HOSPITALS

AT the triennial delegate conference of the Confederation of Health Service Employees held in June, 1956, it was decided by ballot that all mental nurses should ban overtime until their requests for improved salaries and conditions of employment had been met. The main improvements asked for were:

Annual increase of £100 on salaries and allowances for trained nurses, students, and nursing assistants.
A 44-hour standard working week.
Annual leave of 6 weeks for all nurses.
The establishment of a separate Whitley Council for mental nurses.

Since the conference increases of salary and allowances, ranging from £15 to £33, came into effect on July 1, 1957. Hours of duty and annual leave are still under consideration. The Minister of Health has said that he cannot intervene on the question of setting up a separate Whitley Council, which must be left to the decision of the nurses and midwives Whitley Council.

The national executive council of the federation considered that in view of this slow progress it was their duty to implement the ban authorised by the meeting in 1956, but instead of applying the ban nationally they are arranging a token demonstration in selected mental hospitals. A month's ban on overtime was accordingly imposed on Sept. 1 at mental hospitals at Goodmayes (Essex), Bodmin (Cornwall), and Bridgend (Glamorgan); and on Sept. 15 at hospitals at Cheddleton, Lincoln, and Southall. On Sept. 29 it will be imposed on hospitals at Chichester, Gosforth, and Denbigh. The committee will meet on Sept. 24 to select further hospitals at which the ban will be introduced. On Jan. 15 a special delegate conference will be convened to review the position. The executive committee have been criticised by members for not imposing the ban nationally, but they believed that a token demonstration would be more effective. They state, however, that so far "no indication of expediting discussions has yet been indicated from any source."

MONEY FOR DISCOVERY

Now that so many experiments necessitate expensive apparatus and skilled (and paid) assistance, the bounty of such bodies as the Nuffield Foundation performs an invaluable public service. The foundation, which has just issued its report[1] for the year ended last March, administers various funds of which the chief is the Nuffield Fund of £10 million. From the income grants are made for research in science, medicine, sociology (especially the care of old people), and education, throughout the Commonwealth. The introduction to the report makes it clear that the foundation rarely supports conferences, the publication of books, travel, public appeals, or the everyday work of a university department. It is more interested in a promising and well-planned research project, which has not commanded support elsewhere, and "whose originator is imbued with so keen and urgent desire to carry it out that he is ready to struggle along on a shoe-string if misguided grant-giving bodies fail to appreciate his work."

The report shows that many investigators have favourably impressed the foundation. Their work ranges from cytochemistry to population studies, and from a book on the positron (which shows that the principles are interpreted plastically) to an experimental playground in Grimsby. Recent grants include those to Prof. H. J. Eysenck for research into the hypnotic state, to Dr. J. G. L. Williams for an investigation of cardiovascular reactivity as a diagnostic aid in psychiatry, to Dr. J. H. Ottaway for a study on hormone treatment for mongolism, to Dr. J. P. M. Tizard for an electro-encephalographic study of newborn babies, to Dr. Honor Smith and her team for immunological and biochemical investigations of disseminated sclerosis, and to Prof. A. S. Johnstone and Prof. F. W. Spiers for research into means of intensifying fluoroscopic images without increasing the dose of radiation. Various projects are supported which concern rheumatic disease, a special interest of the foundation.

These are but a few of the ways in which the foundation's resources are put to the service of human knowledge and happiness.

OLD PEOPLE ON THE WAITING-LIST

WE have referred[2] to the work of the Hospital Personal Aid Service for the Elderly, which was established in 1951 by King Edward's Hospital Fund. Its purpose is to investigate cases of old people for whom hospital admission is sought, to assess their priority on social grounds, to suggest alternatives

1. The Nuffield Foundation: Twelfth Report. Oxford, 1957. Pp. 161.
2. *Lancet*, 1956, ii, 1147.

to admission where suitable, and to inform the hospital when cases can be removed from the waiting-list.

The service's report for 1956 [3] points out that when a patient is not properly cared for at home, it does not necessarily follow that he should be in hospital, and a social worker may be able to help. In fact, in half the cases investigated the patient's name was removed from the waiting-list, with the family doctor's consent, after he had discussed the case with the hospital. This was sometimes merely a matter of bringing the list up to date by removing names of patients who had died or been admitted elsewhere. Some patients refused admission, or did not need it and refused other kinds of help. For an increasing proportion alternatives have been found —e.g., admission to a local-authority home; provision of meals and home helps and for the lighting of fires on Sundays; or arrangements for a private nurse or admission to a private nursing-home, and raising money from charities to help pay. When patients were recommended for admission, the hospital usually agreed with the service's estimate of priority.

At St. Francis' Hospital, Dulwich, the service helps with a clinic designed to prevent medicosocial breakdown before the patient reaches the waiting-list: thus meals and chiropody were provided for an old man whose sister had gone to hospital.

In conclusion, the report refers to the reluctance of hospitals to discharge patients when their home circumstances are poor, and points out that the circumstances of some patients on the waiting-list are equally poor. Stricter discharge would allow less hardship among those waiting.

ADVANCES ON SELECTED FRONTS

THE Medical Research Council's report for 1955–56 [4] began with two articles on the organisation of research, and thirteen others, each dealing with recent work in a particular field —e.g., lung cancer, filariasis, and abnormal hæmoglobins. These articles have now been reprinted as a pamphlet.[5]

MEDICAL LIBRARIES

A SUBCOMMITTEE [6] of the ten-year-old medical section of the Library Association has compiled a *Directory of Medical Libraries in the British Isles*, which the Association has just published from Chaucer House, Malet Place, London, W.C.1, at the price of 13*s.* to the general public and 9*s.* 6*d.* to its members. It is claimed that this directory includes "all libraries established primarily for use by doctors, medical scientists, or medical students in their professional work. Veterinary and dental libraries are also included but not those devoted to anthropology or the social sciences." Details are given of 147 major libraries, and 396 minor libraries are listed.

University of Leeds

On Thursday, Oct. 10, at 3 P.M., Sir Francis Walshe, F.R.S., will give the inaugural lecture of the faculty of medicine in the Riley Smith Hall. His subject will be the necessary limitations of medical education.

Chadwick Lectures

At 5 P.M. on Thursday, Oct. 31, at the Usher Institute, Warrender Park Road, Edinburgh, 9, Prof. J. H. F. Brotherston will give a lecture on William Pulteney Alison, Scottish pioneer of social medicine. On Thursday, Dec. 5, at 5 P.M., at the Wright-Fleming Institute, St. Mary's Hospital, Norfolk Place, London, W.2, Mr. Ambrose King will give the Malcolm Morris lecture. The title of his lecture will be These Dying Diseases—Venereology in Decline.

University College Hospital Medical School

On Tuesday, Oct. 1, at 2.50 P.M., Dame Janet Vaughan will deliver the opening address of the session.

The annual dinner will be held at the Savoy Hotel, Strand, W.C.2, on Friday, Oct. 18, at 8 P.M. The chair will be taken by Mr. S. Alan S. Malkin. Tickets (£1 12*s.* 6*d.*) may be obtained from the honorary secretary of the old students association of the school, University Street, W.C.1. On Oct. 17 and 18 there will be postgraduate demonstrations for past and present students at the hospital.

3. King Edward's Hospital Fund for London. Hospital Personal Aid Service for the Elderly. Report to Dec. 31, 1956. Obtainable from the office, c/o New Cross General Hospital, London, S.E.14.
4. See *Lancet*, 1957, i, 1347.
5. Current Medical Research. H.M. Stationery Office: 1957. Pp. 56. 2*s.* 6*d.*
6. Messrs. G. J. Hipkins, W. R. LeFanu, L. T. Morton, and J. L. Thornton.

Faculty of Radiologists

The provincial meeting of this faculty will be held in Liverpool on Oct. 5.

Army Medical Advisory Board

Prof. John Bruce has been appointed as a member of the board.

Institute of Cardiology, London

Dr. A. Rae Gilchrist will give the St. Cyres lecture at 1, Wimpole Street, W.1, on Tuesday, Oct. 15, at 5 P.M. His subject will be clinical aspects of high-grade heart-block.

London Jewish Hospital Medical Society

On Thursday, Oct. 3, at 8.30 P.M., Dr. Samuel Sacks will deliver the presidential address to this society at 11, Chandos Street, W.1. He will speak on the Bible in Art.

International Congresses on Tropical Medicine and Malaria

These congresses will be held in Lisbon from Sept. 5 to 13, 1958. Further particulars may be had from the secretary-general, Instituto de Medicina Tropical, Lisbon, Portugal.

Royal Medico-Psychological Association

On Thursday, Nov. 14, at 2 P.M., Sir Wilfrid Le Gros Clark, F.R.S., will deliver the Maudsley lecture at 1, Wimpole Street, London, W 1. His subject will be sensory experience and brain structure.

Royal Eye Hospital, London

Dr. T. H. Whittington will give a course of lectures on refraction work at 5.15 P.M. on Thursdays at the Royal Eye Hospital, St. George's Circus, S.E.1. The first lecture will be on Nov. 21.

Faculty of Homœopathy

A meeting of this faculty will be held at the Royal London Homœopathic Hospital, Great Ormond Street, London, W.C.1, at 5 P.M., on Thursday, Oct. 3, when Dr. F. H. Bodman will read a paper on the treatment of neurosis in childhood.

Northampton Medical Society

The first meeting of this society for 1957–58 will be held on Tuesday, Oct. 1, at 8 P.M., at Northampton General Hospital, when Mr. Charles Gledhill will deliver the presidential address. He will speak on the scope of modern surgery in the treatment of deafness.

Royal Appointment

During the Queen's tour of the United States and Canada her suite will include, as medical officer, Colonel E. H. Ainslie of the Royal Canadian Army Medical Corps. He is senior consultant in the office of the director-general of medical services at Army headquarters, Ottawa.

Middlesex Hospital

The annual dinner of past and present students will be held at the Savoy Hotel, London, W.C.2, on Friday, Oct. 4, at 7.30 P.M. Dr. H. L. Marriott will be in the chair. A refresher course for old students will be held from Oct. 4 to 6 at the medical school. Further particulars may be had from the secretary of the medical school.

Oliver Bird Trust

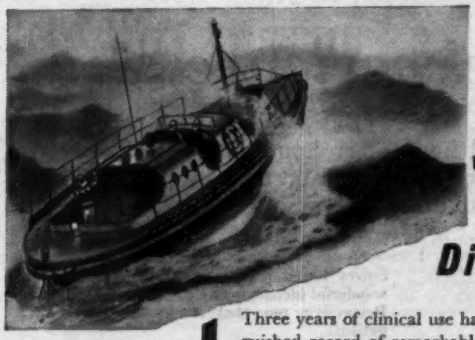
In July, 1957, a charitable fund was established with this title. The trustees are Mrs. M. A. Pyke, Mrs. Burrell, and Mr. A. S. Parkes, SC.D., F.R.S. Its object is "the advancement of knowledge of methods of fertility control with special reference to the promotion and provision of facilities for tests and clinical trials of systemic methods of contraception as they become available, and in the meantime for the improvement of locally acting spermicides." Immediate steps being taken by the trustees include:

The offer in each of the next five years of an Oliver Bird prize for laboratory or clinical work bearing on the control of conception. The prize will consist of a cash award of not less than £250 and the Oliver Bird medal for the year. Application for the first prize should be made not later than Dec. 31 of this year.

The arrangement annually of two Oliver Bird lectures—a background lecture, to promote in medical and scientific circles recognition of the importance of investigating fertility control, and a technical lecture, sponsored by the Society for the Study of Fertility, on scientific aspects of the technical problem. The first of the technical lectures will be given on Wednesday, Nov. 6, by Dr. T. Mann, F.R.S., on the biochemical basis of spermicidal activity.

The setting up of a Council for the Investigation of Fertility Control, which will work with the Family Planning Association and will be responsible for organising tests and clinical trials.

The office of the Trust is at 64, Sloane Street, London, S.W.1.



Distinguished Record

Three years of clinical use have given 'Ilotycin' brand Erythromycin a distinguished record of remarkable safety. Highly effective against staphylococci, streptococci and pneumococci, 'Ilotycin' exerts negligible effect on the colon bacillus and does not give rise to the extremely dangerous staphylococcal enterocolitis. It is particularly valuable against penicillin-resistant staphylococci and has become the logical first choice antibiotic after penicillin.

'Ilotycin' is the surest and safest way of combating a wide range of common infections encountered in general and hospital practice, and can be life-saving in overwhelming infections where prompt response is vital.

The average daily dose is 1 Gm., increased in severe infections.

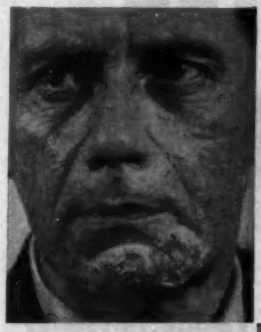
'Ilotycin' is available as Tablets of 100 mg. and 250 mg., and as 'Ilotycin' Paediatric for oral suspension.

Lilly

'ILOTYCIN'

Originated by Lilly

ELI LILLY AND COMPANY LIMITED, BASINGSTOKE, ENGLAND



℞ F99 for

OINTMENT
CAPSULES
LIQUID

ECZEMA VARICOSE ULCERS FURUNCULOSIS

Diagnosis: Obstinate eczema of the face. Photograph taken before treatment with "F99".

Photograph taken after 18 weeks' treatment with one "F99" capsule and one application of "F99" ointment daily.

It has been shown beyond question by large scale serum-lipids studies that a good proportion of patients suffering from intractable skin conditions have a deficiency of the essential fatty acids. It is not possible to carry out these studies in everyday practice, but any patient with eczema or furunculosis who fails to respond to symptomatic treatment should most certainly be tried with essential fatty acids "F99." A high proportion of these patients will be found to respond.

In gravitational ulcers, where the skin is "undernourished," the application of additional essential fatty acids rarely fails to heal the wound.

Literature on request

INTERNATIONAL LABORATORIES LTD. *Dept. LT35*, 205, HOOK ROAD, CHESSINGTON, SURREY

I know from experience . . .

"HAVE you ever laid in bed hour after hour with nothing to do but think or doze . . . too weak to talk to your nearest bed-fellow . . . unable to read, and only the sky or ceiling to look at?

I know from my own experience as a patient in a Surrey hospital, that a Pillowphone radio is a wonderful blessing and a definite aid to recovery. Remember, too, that it cannot disturb other patients.

Will you use your influence or authority to help in increasing the number of Pillowphones in the hospital in which you serve?"

S. G. BROWN PILLOWPHONES are waterproof, can be sterilised and are interchangeable with existing standard type headphones.

Please write or telephone for full details.

S. G. Brown, Ltd.

Shakespeare St., Watford, Herts.

Telephone: Watford 7241.

AMPHETONE

REGISTERED

A GENERAL STIMULANT FOR THE CENTRAL NERVOUS SYSTEM

For cases requiring a quick-acting general stimulant without increasing the patient's appetite, we consider Amphetone unique. It combines for the first time, Dexamphetamine Sulphate and Strychnine with Glycerophosphates and members of the Vitamin B Group. The Dexamphetamine provides the convalescent with an immediate feeling of well-being, this being followed by the well-known tonic effects of the other medicaments. Clinical reports have been excellent.

FORMULA

Dexamphetamine Sulphate B.P.C., 1/12 grain: Strychnine Hydrochloride B.P., 1/60 grain: Calcium Glycerophosphate B.P.C., 2 grains: Sodium Glycerophosphate B.P.C., 2 grains: Aneurine Hydrochloride B.P., 1/30 grain: Nicotinamide B.P., 1/4 grain: Riboflavin B.P., 1/60 grain: Syrup of Blackcurrant B.P.C., 2 fluid drms.: Water, to 1/2 fluid ounce.

POISON | 54

Available in bottles containing 10, 20 40 and 80 fluid ounces. Professional prices 5/3, 9/11, 16/8 and 30/4 each. Samples available on request.

JAMES WOOLLEY, SONS & CO. LTD., VICTORIA BRIDGE, MANCHESTER 3

In association with J. C. Arnfield & Sons, Ltd.

London Stockists: May, Roberts & Co., Ltd., 47, Stamford Hill Road, London, N.16.

Distributors for Northern Ireland: Messrs. Dobbin & Stewart, 47-49, Earl Street, Belfast.

WAI

THE DISTILLERS COMPANY LIMITED

EXCERPTS FROM THE CHAIRMAN'S STATEMENT TO SHAREHOLDERS

BIOCHEMICALS DIVISION NOW REPRESENTED IN OVER NINETY EXPORT MARKETS

ACCOUNTS.—The trading profit for the year, after charging depreciation, amounted to £21,432,602, compared with £19,584,795 last year. Our income from trade investments was also higher, at £1,259,306 against £1,018,441, mainly through receiving a first dividend on our investment in Murgatroyd's Salt & Chemical Company Limited. After charging interest on loans, the profit before taxation was £22,452,798, an increase of £2,141,368.

In view of the very favourable results achieved, and despite the fact that the greater part of the higher profit has been absorbed by taxation, your Directors feel that a moderate increase in dividend is justified. They therefore recommend that the final dividend on the Ordinary Capital should be at the rate of 10½d. per share of 6s. 8d., which, with the interim already paid of 4½d. per share, makes 1s. 3d. per share for the year, or 18¾%, as compared with 17½% last year.

Scotch Whisky

We have had a full and satisfactory distilling season, with production at a higher level than last year.

As the stock position of the industry has improved, so it has been possible for it to expand sales both at home and in export markets.

Since the war there has been a continuous increase in the world-wide demand for Scotch Whisky, although in certain markets there are now indications that supplies are not far from meeting the demand. The industry's stock position represents a coverage of approximately eight years at the present level of sales. This in itself is not an excessive figure, but judgment and care will need to be exercised in planning for the future, to ensure that the distilling programme is reasonably related to the anticipated future demand for Scotch Whisky, and that the stocks which the industry are laying down do not prove to be more than adequate.

At the present time, however, the outlook is encouraging, and the popularity of our brands in all markets is the best testimony to the soundness of our policy of fully maintaining the quality of our products during the post-war years. In the event of more competitive conditions developing, this policy in regard to quality should stand us in good stead.

The increase in our stocks has necessitated an extensive programme for the construction of additional warehouse accommodation, which is now in progress. At the same time, the work of reconstruction and modernisation of certain of our distilleries and large bottling and blending establishments is proceeding satisfactorily.

Gin

The sales of our Gin Companies have again shown a very satisfactory increase, although our export trade is becoming more difficult, largely due to the fact that many countries are now producing locally made gin.

Yeast

During the year, our sales of yeast in the United Kingdom were reasonably well maintained, in spite of increased competition, particularly from foreign imports.

INDUSTRIAL GROUP

The products manufactured by the Divisions and Companies comprising the Industrial Group show for the most part an increase in the volume of sales, and the past year has been one of general progress. Although we have adhered to a policy of price restraint and have had to meet higher raw material costs, increased efficiencies and turnover have enabled the Group to show further improvement in earnings.

The chemical and plastics industries continue to expand vigorously, particularly in materials derived from petroleum, and the past year has seen the completion of extensions and the launching of new projects which should add significantly to your Company's position in these fields and its future earning power.

General Chemical Division. Despite a sharp fall in sales to some of the major consuming industries, notably the motor car industry, our over-all home sales of synthetic organic chemicals and solvents showed a small expansion during the year and exports also increased.

As already indicated, raw material, fuel and also labour costs continued their upward trend. A major problem was the sudden substantial increase in the price of molasses, from which an important part of our industrial alcohol requirements is produced. Fortunately, the timely completion of British Hydrocarbon Chemicals' extensions at Grangemouth for the production of synthetic industrial alcohol from petroleum enabled the Company to cushion the full impact of the higher molasses price on our consumers of industrial alcohol.

At Hull, the vinyl acetate plant of our associated Company, Hedon Chemicals Limited, was commissioned on time. Market conditions are competitive, but sales are developing satisfactorily.

Despite the poor summer last year, and the consequent contraction of the traditional outlets in the beverage and ice cream trades, total sales of carbon dioxide continued to expand rapidly, owing to the extended use of this material in industrial fields. In view of the large programme contemplated for the construction of nuclear power stations, it is of interest to record that the carbon dioxide equipment required at Calder Hall was designed and installed by your Company, which is one of the main suppliers of this product.

British Hydrocarbon Chemicals Limited, Grangemouth. As already stated, the major ethylene and alcohol plants of British Hydrocarbon Chemicals Limited were successfully commissioned, and doubled the then existing capacities.

The new butadiene plant is also in full operation. The entire output is being sold for the production of synthetic rubbers and similar polymers. In addition, the plant for the manufacture of propylene tetramer, the main raw material for detergent alkylates, has been completed and is now in operation.

Grange Chemicals Limited, a subsidiary manufacturing detergent alkylate required in the production of synthetic soaps, has had a successful first year, and is now producing a very high grade product at well above designed output.

Forth Chemicals Limited, also a subsidiary, has completed its major extension for the manufacture of monomeric styrene, and is operating successfully. This Company is now able to supply the present entire domestic usage of monomeric styrene and sales are at a high level.

Your Company has sub-licensed to British Hydrocarbon Chemicals the exclusive rights which we hold from the Phillips Petroleum Company of U.S.A for the production of low pressure high density polyethylene by an improved process, and a plant with an annual capacity of 12,000 tons is now under construction. The fields of application for polyethylene are constantly expanding, and the special material to be produced should be readily absorbed in this growing market.

BIOCHEMICAL DIVISION

The year under review has shown even keener competition in what may be termed the basic antibiotics—namely Penicillin and Streptomycin. The trend towards better prices to which I referred last year has not progressed as far as expected, and the competitive conditions in many markets leave very little margin. Continuous research leading to improvement in yields has helped us to maintain our position, and the extension of our range of products has enabled this Division to show reasonably satisfactory profits. I referred last year to the successful introduction of a new form of Penicillin —Distaquaine V—which for the first time made Penicillin available in a safe, effective form for administration by mouth. This product is now well established and is in great demand. Licences under our exclusive manufacturing rights have been granted to three other leading British pharmaceutical houses on suitable terms.

The reorganisation of our selling arrangements, both at home and abroad, has become fully operative during the year, with encouraging results, and the division is now represented in over ninety export markets.

Plastics Division. Our sales during part of the year inevitably reflected the credit squeeze and the recession in the motor industry. The demand in the latter part of the year, however, showed encouraging growth, which still continues although there is keen competition in certain materials. We are securing increasing sales of "Geon" polyvinyl chloride, "Styron" polystyrene and the "Epok/Cellomold" range of synthetic resins and moulding powders. The raw materials for these products are mainly supplied by associated companies within the Distillers Group.

By arrangement with B. F. Goodrich Chemical Company, U.S.A., British Geon is now constructing a new plant at Barry, South Wales, for the manufacture of oil-resistant synthetic rubbers and latices, which will be marketed under the registered trade mark "Hycar." These materials are at present imported from the U.S.A., and the growing demand for them in this market gives every assurance of our being able to dispose of the output of the new plant.

Murgatroyd's Salt & Chemical Company Limited. This Company had a good year and was able to sell its entire output of its main products, chlorine and caustic soda, at satisfactory prices. On the other hand, salt was a difficult market, and sales and realisations were somewhat lower, due to intense Continental competition. It will be recalled that a substantial financial interest in this Company was acquired to meet the needs of British Geon Limited for chlorine, used in the manufacture of polyvinyl chloride, and I am glad to say that its total requirements are now being met by the Murgatroyd Company.

Magnesium. Our associated company, Magnesium Elektron Limited, had a very good year in sales of magnesium and its alloys. Our subsidiary, F. A. Hughes & Company Limited, which has developed jointly with Magnesium Elektron Limited the new cathodic protection of metals against corrosion by the use of magnesium anodes, has had an outstandingly successful year in the installation of its "Guardion" system in ships, particularly tankers. The efficacy of this anti-corrosion method is receiving widespread recognition, and this is reflected in the record sales achieved.

SOUTH AFRICA.—National Chemical Products Limited, our associated company, has continued to make good progress, and the expansion programme to which I referred last year has made a valuable contribution to the year's trading. The over-all results are most encouraging, reflecting increased turnover and earnings.

AUSTRALIA.—The trading results of our associated company, C. S. R. Chemicals Pty. Limited, showed a further improvement during the past year. This is partly due to the bounty granted by the Australian Government on the production of cellulose acetate flake, but increased turnover in this material and improved efficiencies have made their contribution, whilst the expansion of the general chemical and plastics division has made notable progress.

TECHNICAL DEVELOPMENT

For many years your Company has spent large sums on research and development, the scale of which is in step with similar organisations, both in the United Kingdom and U.S.A. This is an essential background to progress in the industries in which we operate, and, judged on past results, your Directors are satisfied that a continuance of this policy is essential to enable your Company to maintain its position and take full advantage of opportunities for further development.

FUTURE PROSPECTS

So far, the current year's results continue to be favourable, although in many markets trading conditions tend to become increasingly competitive. However, world trade continues to expand, and, subject to any major set-back, I feel confident that the broad spread of our operations will stand us in good stead and enable your Company to continue its progress.

ST. ANDREW'S HOSPITAL

FOR NERVOUS AND MENTAL DISORDERS

NORTHAMPTON

PRESIDENT: THE EARL SPENCER

MEDICAL SUPERINTENDENT: THOMAS TENNENT, M.D., F.R.C.P., D.P.H., D.P.M.

This Registered Hospital is situated in 130 acres of park and pleasure grounds. Voluntary patients, who are suffering from incipient mental disorders or who wish to prevent recurrent attacks of mental trouble; temporary patients, and certified patients of both sexes are received for treatment. Careful clinical, biochemical, bacteriological, and pathological examinations. Private rooms with special nurses, male or female, in the Hospital or in one of the numerous villas in the grounds of the various branches can be provided.

WANTAGE HOUSE

This is a Reception Hospital in detached grounds with a separate entrance, to which patients can be admitted. It is equipped with all the apparatus for the complete investigation and treatment of Mental and Nervous Disorders by the most modern methods: insulin treatment is available for suitable cases. There is an Operating Theatre, a Dental Surgery, an X-ray Room, an Ultraviolet Apparatus, and a Department for Diathermy and High-frequency treatment. It also contains Laboratories for biochemical, bacteriological, and pathological research. Psychotherapeutic treatment is employed when indicated.

MOULTON PARK

Two miles from the Main Hospital there are several branch establishments and villas situated in a park and farm of 650 acres. Milk, meat, fruit, and vegetables are supplied to the Hospital from the farm, gardens, and orchards of Moulton Park. Occupational therapy is a feature of this branch, and patients are given every facility for occupying themselves in farming, gardening, and fruit growing.

BRYN-Y-NEUADD HALL

The seaside house of St. Andrew's Hospital is beautifully situated in a park of 330 acres, at Llanfairfechan, amidst the finest scenery in North Wales. On the North-West side of the Estate a mile of sea coast forms the boundary. Patients may visit this branch for a short seaside change or for longer periods. The Hospital has its own private bathing house on the seashore. There is trout-fishing in the park.

At all the branches of the Hospital there are cricket grounds, football and hockey grounds, lawn tennis courts (grass and hard courts), croquet grounds, golf courses, and bowling greens. Ladies and gentlemen have their own gardens, and facilities are provided for handicrafts, such as carpentry, etc.

For terms and further particulars apply to the Medical Superintendent (TELEPHONE: Northampton 4354 (3 lines)), who can be seen in London by appointment.

CLIFFDEN, TEIGNMOUTH

For the early treatment of nervous disorders and patients needing rest and care

A well-appointed House with spacious balconies and extensive views of the South Devon Coast. Beautiful garden and own dairy in 35 acres in the same grounds, **ROWDENS**, a comfortable house with lovely views. Private road to the beach

There is also a charming house, **EBWORTHY, MANATON, DARTMOOR**, situated in 25 acres, 1100 ft. up for bracing moorland air

Resident Physicians—BERTHA M. MULES, M.D., B.S., ANNE S. MULES, M.R.C.S., L.R.C.P. *Telephones*—TEIGNMOUTH 289 and 537

CHISWICK HOUSE

PINNER, MIDDLESEX

Telephone: PINNER 234

A private Nursing Home for patients suffering from all forms of Nervous and Psychological illness. Forty-four patients of both sexes. A certain number of elderly patients received. All modern forms of treatment. Psychotherapy, Electroplexy, Modified Insulin, etc. Two country houses in adjoining grounds of 5 and 6 acres each respectively, 12 miles north-west of London. Frequent trains Baker Street Station to Pinner. One-quarter of a mile from Pinner Station.

Apply to the Medical Director, DOUGLAS MACAULAY, M.D., D.P.M.

HEIGHAM HALL, NORWICH

PRIVATE MENTAL HOME for Nervous and Mental illness. All types of treatment carried out. Accommodation for Alcoholics and Addicts available. Special Geriatric Unit now open. Fees from 7 gns. per week upwards according to requirements.

Apply to Dr. J. A. SMALL Telephone: Norwich 20080

WYKE HOUSE HOSPITAL

ISLEWORTH, MIDDLESEX

Telephone: EALing 7000

A private home for the individual treatment of all forms of nervous and mental illness, including alcoholism.

H. PULLAR-STRECKER, M.D. G. W. SMITH, O.B.E., M.B., CH.B.

NORTHUMBERLAND HOUSE

Psychiatric Nursing Home

235-7 BALLARDS LANE, N.3 Tel.: FINchley 528

Resident Med. Director Dr. R. M. RIGGALL, Mem. Brit. Psycho-Analytical Socy.

Deep insulin coma unit, psychotherapy, etc.

THE MEDICAL PROTECTION SOCIETY LIMITED

Over 60 years experience in medical defence and protection

Complete indemnity granted to members in cases undertaken on their behalf

ANNUAL SUBSCRIPTION: £1 for first three years for newly qualified entrants and £2 thereafter

Full particulars from the Secretary (Dr. Alistair French), **Victory House, Leicester Sq., W.C.2.** Gerrard 4553 and 4814

Vacancies

ACADEMIC AND EDUCATIONAL SECTION *Page* 34

ANÆSTHETICS

Middlesex, W.1. Sr. Reg. 35
Royal Free Hosp. Group. Sr. H.O. .. 36
Kettering Gen. Sr. H.O. 39
Liverpool United Hosps. Reg. .. 39
Luton & Dunstable. Reg. 39
Newcastle R.H.B. Locum Sr. Reg. or Reg. & Reg. 40
Oxford R.H.B. Cons... 35
Oxford R.H.B. Reg. 41
Romford. Oldchurch. Sr. H.O. .. 41
South Cheshire H.M.C. Sr. H.O. .. 42
Tunbridge Wells. Pembury. Sr. H.O. 42
Winchester & Lord Mayor Treloar Groups. Reg. 43
Worcester. Ronkswood. Locum Sr. H.O. 42
U.S.A. Cambridge, Mass. Residencies 43

BACTERIOLOGY

Royal Free, W.C.1. Sr. Reg... .. 36

CARDIOLOGY
National Heart (Maids Moreton, Bucks). Sr. H.O. 35

CASUALTY
Connaught, E.17. Sr. H.O. 35
Hackney, E.9. H.O.'s 35
Metropolitan, E.8. Sr. H.O. 35
Queen Mary's Hosp. for the East End, E.15. H.O. 36
Blackburn. Royal Infy. Jr. H.M.O.'s or Sr. H.O.'s 37
Bolton & Dist. H.M.C. Sr. H.O. .. 37
Cardiff. St. David's. Sr. H.O. .. 38
Colchester Group H.M.C. Sr. H.O.'s 38
Derby. Derbyshire Royal Infy. Sr. H.O. 38
Grimsby Gen. Sr. H.O. 39
Hastings. Royal East Sussex. Locum Sr. H.O. 39
Leamington Spa. Warneford Gen. Sr. H.O. 39
Slough. Upton. Sr. H.O. 41
Taunton & Somerset. Sr. H.O. .. 42
Watford & Dist. Peace Mem. Sr. H.O. 43

CHEST AND TUBERCULOSIS
Brompton, S.W.3. H.O.'s 35
Highlands Gen., N.21. Sr. H.O. .. 35
London Chest, E.2. Reg. 35
Barnsley Chest Service. Reg. .. 36
Benenden Chest Hosp. Sr. H.O. .. 36
Glasgow Northern Hosps. B.O.M. Jr. H.M.O.'s 38
Halifax. Northowram Hall. Sr. H.O. 39
Ilkley. Middleton. Jr. H.M.O. .. 39
Lanark. Bellefield San. Jr. H.M.O... 39
Leeds R.H.B. Reg. 39
Manchester R.H.B. Sr. Reg. 40
Northampton. Creaton. Sr. H.O. .. 40
Oxford United Hosps. Reg. 41
Skipton. Grassington. Sr. H.O. .. 41
Watford Chest Clinic. Reg. & Locum Reg. 43
York. Fairfield San., City & County Hosps. Sr. H.O. 43

DENTAL SURGERY
Royal Northern, N.7. P.-t. Clin. Asst. (G.P.). 36

DERMATOLOGY
French Hosp. & Dispensary, W.C.2. Hon. Dermatologist 34

EAR, NOSE AND THROAT
St. Mary's, W.2. Sr. Reg. 36
Ashton, Hyde & Glossop H.M.C. Sr. H.O. 36
Birmingham R.H.B. Reg. 37
Dudley, Stourbridge & Dist. P.-t. Clin. Asst. 38
Nottingham Gen. Sr. H.O. 40
Shrewsbury. Eye, Ear & Throat. Sr. H.O. 41

GERIATRICS
Brighton Gen. H.O. 37
Chesterfield. Scarsdale. Jr. H.M.O... 38
Halifax. St. John's. Sr. H.O. .. 39

INFECTIOUS DISEASES
Glasgow Northern Hosps. B.O.M. Jr. H.M.O.'s 38
Ipswich. St. Helen's. H.O. 39
Lancaster. Beaumont. Sr. H.O. .. 39
Leeds R.H.B. Reg. 39
Leeds. Seacroft. Sr. H.O. 39
Portsmouth Group H.M.C. Sr. H.O. 41

MEDICINE
West London, W.6. H.O.'s 36
Alexandria, Dunbartonshire. Vale of Leven. H.O. 36
Bedford Gen. Reg. 37
Beverley. Westwood. H.O. or Sr. H.O. 37
Birmingham United Hosps. Reg. .. 37
Driffield. East Riding Gen. H.O. .. 38
Exeter Clinical Area. Cons. 34
Hitchin. Lister. Reg. 39
Ipswich & East Suffolk. Pre-reg. H.O. 39
Leeds R.H.B. Reg. 39
Lincoln. St. George's. Pre-reg. H.O. or Sr. H.O. 39
Liverpool. Bootle. H.O. 39
Maidenhead. Pre-reg. H.O. 40
Romford. Victoria. H.O. 41
Scotland. Western R.H.B. P.-t. Cons. 35
Sheffield United Hosps. & R.H.B. Sr. Reg. 41
Shrewsbury. Royal Salop Infy./ Copthorne. H.O. 41
Southampton. Royal South Hants. H.O. 41
St. Albans City. H.O. 42
Stoke-on-Trent. City Gen. H.O.'s .. 42
Taplow. Canadian Red Cross Mem. Reg. 42
Taunton & Somerset. Sr. H.O. .. 42
Wolverhampton. New Cross. Pre-reg. H.O. 43

NEUROLOGY
National Hosps. for Nervous Diseases. Sr. Reg. 36

OBSTETRICS AND GYNÆCOLOGY
British Hosp. for Mothers & Babies, S.E.18. H.O. 35
Barnsley. St. Helen. Reg. 36
Birmingham. Dudley Road. H.O. .. 37
Brighton & Lewes H.M.C. H.O. .. 37
Cardiff. St. David's. H.O. 38
Chelmsford. St. John's. H.O. .. 38
Doncaster. Western. Reg. 38
Lincoln. St. George's. Sr. H.O. .. 39
Oxford R.H.B. Sr. Reg. 41
Reading Combined Hosps. H.O. .. 41
Rochdale & Dist. H.M.C. H.O. .. 41
Scotland. Western R.H.B. Reg. .. 41
Shrewsbury. Royal Salop Infy & Copthorne. Sr. H.O. 41
South East Met. R.H.B. P.-t. Cons. 35
Stoke-on-Trent. City Gen. Sr. H.O. 42
Stoke-on-Trent. North Staffs Royal Infy. Sr. H.O. 42
Winchester. Royal Hants County. H.O. 43
Dublin. St. Kevin's. Regs. 43

OPHTHALMOLOGY
Birmingham & Midland Eye. H.O. .. 37
Newcastle H.M.C. Sr. H.O. 40
Romford Group H.M.C. P.-t. Clin. Asst. 41
Romford. Oldchurch. Sr. H.O. .. 41
Scotland. Western R.H.B. Sr. Reg... 41

ORTHOPÆDICS
Royal National Orthopædic (Stanmore). Sr. H.O.'s 36
Beverley. Westwood. H.O. 37
Caerphilly. Pre-reg. H.O. 37
Cardiff. Prince of Wales Orthopædic. Sr. H.O. 38
Cardiff United Hosps. Reg. 37
Carmarthen. West Wales Gen. Sr. H.O. 38
Colchester Group H.M.C. H.O. .. 38
Durham County. Sr. H.O. & H.O... 38
Glasgow. Victoria Infy. Sr. H.O. .. 38
Ipswich & East Suffolk. Sr. H.O. .. 39
Leeds R.H.B. P.-t. Cons. 34
Manchester R.H.B. Locum Reg. .. 40
Manchester R.H.B. Reg. 40
Newcastle R.H.B. Reg. 40
Nottingham Gen. Sr. H.O. & Locum 40
Southampton. Royal South Hants. H.O. & Sr. H.O. 41
Sheffield R.H.B. Sr. H.M.O. 35
Winchester. Royal Hants County. Sr. H.O. 43

PÆDIATRICS
Hosp. for Sick Child., W.C.1. Sr. H.O. 36
Queen Elizabeth Hosp. for Child. M.C. H.O.'s 36
Birmingham. Little Bromwich Gen. H.O. 37
St. Albans City. H.O. 42
Stockport. Stepping Hill. Sr. H.O. .. 42
Stoke-on-Trent. City Gen. Pre-reg. H.O. 42
Swindon & Dist. H.M.C. Sr. H.O. .. 42
Wigan. Royal Albert Edward Infy. Sr. H.O. 43

PATHOLOGY
Beverley. Westwood. Sr. H.O. .. 36
Enfield. Chase Farm. Sr. H.O. .. 38
Newcastle R.H.B. Sr. Reg. 40
Nottingham City. Sr. H.O. 40
Scotland. Western R.H.B. Reg. .. 41
Woking & Chertsey Group Lab. Sr. H.O. 42

PHYSICAL MEDICINE
Buxton. Devonshire Royal. Sr. H.O. 37
Manchester R.H.B. Reg. 40

PLASTIC SURGERY
Manchester R.H.B. Reg. 40
Manchester. Wythenshawe. Locum Sr. H.O. 40

PSYCHIATRY
Bolton & Dist. H.M.C. Sr. H.O. .. 37
Chesterfield H.M.C. Jr. H.M.O. .. 38
Glasgow. Hawkhead (Mental). Sr. H.O. 38
Newcastle R.H.B. Sr. H.M.O. .. 35
North West Met. R.H.B. Cons. .. 35
Norwich. St. Andrew's. Sr. H.O. .. 40
Scotland. Western R.H.B. Sr. H.M.O. 35
Sheffield R.H.B. Sr. Reg. 41
Southall. St. Bernard's Hosp. for Nervous & Mental Disorders. Sr. H.O. 41
South East Met. R.H.B. Sr. Reg. .. 42
South-Western R.H.B. Cons. .. 35
St. Albans. Cell Barnes. Reg. .. 42
Warwick. Central Mental. Sr. H.O... 43
Welsh R.H.B. Sr. H.M.O. 35
Wigan. Billinge. Reg. 42
Worcester. Powick. Jr. H.M.O. .. 42
U.S.A. Virginia. Physicians 35

RADIOLOGY
National Hosps. for Nervous Diseases. Reg. 36
South East Met. R.H.B. P.-t. Cons. .. 34
East Anglian R.H.B. Reg. 38
Liverpool R.H.B. Sr. H.M.O. .. 34
Manchester R.H.B. Locum P.-t. Cons. 34
Northwood. Mount Vernon. Reg. .. 40
Scotland. Western R.H.B. Sr. Reg. & Reg. 41
Sheffield R.H.B. P.-t. Cons. 35
Sheffield United Hosps. Reg. 41

RADIOTHERAPY
Royal Northern, N.7, & Prince of Wales's, N.15. Sr. H.O. (Trainee).. 36

SURGERY
Central Middlesex, N.W.10. H.O. .. 35
North Middlesex, N.18. H.O. 36
St. Mark's, E.C.1. Sr. Reg. or Reg. .. 36
Ashington. H.O. & Locum Jr. H.M.O. 36
Barnstaple. North Devon Infy. H.O. 36
Birmingham R.H.B. Regs. 37
Birmingham United Hosps. Reg. .. 37
Bishop's Stortford. Herts & Essex Gen. Sr. H.O. & H.O. 37
Bournemouth. Christchurch. Sr. H.O. 37
Brighton. Royal Sussex County. Pre-reg. H.O. 37
Burton-on-Trent Gen. Pre-reg. H.O. 37
Caernarvon & Anglesey H.M.C. H.O.'s 37
Chichester. Royal West Sussex. H.O. 38
Doncaster Royal Infy. Pre-reg. H.O. or Sr. H.O. 38
Dudley, Stourbridge & Dist. Pre-reg. H.O. 38
Edgware Gen. H.O. 38
Exeter. Royal Devon & Exeter. H.O.'s 38
Hereford Gen. Pre-reg. H.O... .. 39
Hove Gen. Pre-reg. H.O. 39
Huddersfield Royal Infy. H.O. .. 39
Hull. Kingston Gen. Pre-reg. H.O. 39
Kendal. Westmorland County. Jr. H.M.O. 39
Leamington Spa. Warneford Gen. H.O. 39
Luton & Dunstable. Locum Reg. .. 39
Manchester R.H.B. Regs. 40
Manchester. Royal Manchester Child's. • H.O. 40
Morecambe. Queen Victoria. Sr. H.O. 40
Nottingham City. H.O. 40
Reading. Battle. H.O. 41
Salford Royal. Sr. H.O. 41
Scotland. Western R.H.B. Reg. .. 41
Sheffield R.H.B. P.-t. Cons. 35
Shrewsbury. Royal Salop Infy./ Copthorne. H.O. 41
Southampton. Royal South Hants. H.O. 41
St. Albans City. H.O. 42
Stoke-on-Trent. City Gen. Pre-reg. H.O. 42
Torquay. Torbay. Sr. H.O. 42
Tredegar Gen., Mon. Jr. H.M.O. .. 42
Welsh R.H.B. Regs. 42
Wolverhampton. New Cross. Pre-reg. H.O. 43

THORACIC SURGERY
Royal Masonic, W.6. Cons. 34
South East Regional Thoracic Surgery Unit, S.E.18. Sr. H.O. 36
Bristol. Coombe & Frenchay H.M.C. Sr. H.O. 37
Manchester R.H.B. Reg. 40
Sully, Glam. Sr. H.O... 42

UROLOGY
St. Peter's, St. Paul's & St. Philip's, W.C.2. Sr. Reg. 36

PUBLIC APPOINTMENTS 43
GENERAL PRACTICE 44
NON-MEDICAL 44
MISCELLANEOUS 44

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Academic and Educational

ROYAL COLLEGE OF PHYSICIANS

JOSEPH SENIOR WHITE TRUST

Applications are invited for a JOSEPH SENIOR WHITE RESEARCH FELLOWSHIP value not less than £1250 a year. Existing superannuation arrangements may be continued. The Fellowship is for a period of 1 year, renewable up to a total period of 3 years. Under the terms of the Fund the Fellow appointed must engage in scientific research solely with a view to the discovery of means to alleviate human suffering and for the prevention and cure of diseases.

Applications, accompanied by the names of 2 referees, should state details of the proposed work, under whom it is proposed to undertake the work and the name of the institution where the work is to take place. A grant for reasonable expenses may be paid to the institution concerned.

Application forms and further details may be obtained from the Assistant Registrar, Royal College of Physicians, Pall Mall East, London, S.W.1, by whom applications for a Fellowship must be received not later than 1st January, 1958.

UNIVERSITY OF MANCHESTER

A SHORT INTENSIVE COURSE in the PRACTICE OF INDUSTRIAL MEDICINE will be held in the Department of Occupational Health, Manchester University, commencing MONDAY, 28TH OCTOBER to SATURDAY, 2ND NOVEMBER, inclusive. Numbers will be strictly limited. Registration fee £7 7s.

Applications should be sent to the Secretary, Nuffield Department of Occupational Health, Clinical Sciences Building, Workplace, Manchester, 13, from whom further particulars may be obtained.

COURSE IN ADVANCED MEDICINE

A POSTGRADUATE COURSE IN MEDICINE will be held at The London Hospital commencing MONDAY, 6TH JANUARY, and finishing FRIDAY, 14TH MARCH, 1958. Classes will be held on Mondays, Wednesdays and Fridays. The course will be limited to 24 students.

The fee for the course will be £25. An entrance fee of £5 5s. must be paid by Non-London Hospital Graduates.

Applications should be made to the Dean.

H. B. MAY, M.A., M.D., F.R.C.P., Dean.

The London Hospital Medical College, Turner-street, E.1.

TANCRED'S STUDENTSHIPS

DIVINITY : MEDICINE : LAW

£100 p.a. each. For men only.

The Governors propose to elect 1 Student in Divinity at Christ's College, Cambridge, on the result of the Scholarship Examinations to be conducted in DECEMBER, 1957, by the Queen's, Christ's, St. John's, Emmanuel and Sidney Sussex Group of Colleges in the University of Cambridge.

Candidates must have been born in England, Scotland or Wales and be members of the Church of England and unmarried; they must also be within the ages of 17 and 22 years.

Candidates should in addition to making the necessary arrangements with the Managers of the above Scholarship Examinations send in a Petition to the Clerk to the Tancred Foundation by 1st November, 1957.

The Foundation also awards Studentships in Physic and Law, further details of which will be published in this paper at a later date.

Apply for further particulars and form of Petition stating kind of Studentship and mentioning this paper to the Clerk, R. M. C. HOWARD, Esq., D.S.O., 28, Lincoln's Inn-fields, London, W.C.2.

SOCIETY OF APOTHECARIES OF LONDON

DIPLOMA IN INDUSTRIAL HEALTH

The next Examination will begin on MONDAY, 9TH DECEMBER, 1957. The following Examination will be held in July, 1958.

For Regulations apply Registrar, Apothecaries' Hall, Black Friars-lane, London, E.C.4.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL (UNIVERSITY OF LONDON), Denmark-hill, S.E.5. Applications are invited for the ROUSSEL RESEARCH FELLOWSHIP IN STEROID ENDOCRINOLOGY tenable in the Medical School. The successful applicant, who must be an Australian and should be suitably qualified in medicine or a branch of medical science, will be expected to undertake research on adrenal endocrinology in relation to human disease. The Fellowship will be full-time, tenable for 1 year in the first instance, but will be renewable to a maximum of 3 years. The salary will be £1200 (sterling) per year. The cost of the Fellow's return fare from Australia will be paid by Roussel Laboratories Ltd.

Further particulars may be obtained from the Professor of Chemical Pathology, to whom applications, giving full particulars of age, qualifications and experience, together with the names of 3 referees, should be sent so as to reach him before Saturday, 26th October, 1957.

THE UNIVERSITY OF LIVERPOOL. Department of STUDIES IN PSYCHOLOGICAL MEDICINE. Applications are invited for the post of RESEARCH ASSISTANT IN PSYCHOLOGICAL MEDICINE at a salary within the range £1000–£1300 p.a., according to qualifications and experience. The appointment will be tenable for 1 year and may be renewed for a second year.

Applications, stating age, academic qualifications and experience, together with proposed subjects of research and the names of 3 referees, should be received not later than 19th October, 1957, by the Registrar, from whom further particulars of the conditions of appointment may be obtained.

UNIVERSITY OF CAPE TOWN. Provincial Administration OF THE CAPE OF GOOD HOPE. Joint Medical Staff. Applications are invited for the post of SENIOR LECTURER IN PHYSIOLOGY. The appointment will be made under the terms of the Joint Staff agreement between the University of Cape Town and the Provincial Administration of the Cape of Good Hope. The successful candidate will take part in the teaching of medical and science students and will be responsible for the experimental laboratories. The salary is £1980 p.a. plus a temporary cost-of-living allowance for a married man (at present £234 p.a.).

Applicants should state age, qualifications, experience, publications and research interests and give the names of 2 referees whom the University may consult. 2 copies of the application must reach the Secretary, Association of Universities of the British Commonwealth, 36, Gordon-square, London, W.C.1 (from whom a memorandum giving the conditions of appointment should be obtained), by 7th November, 1957. A third copy must be sent by air-mail to the Registrar, University of Cape Town, Private Bag, Rondebosch, Cape Town, South Africa by the same date.

The University reserves the right to appoint a person other than 1 of the applicants or else to make no appointment.

Hospital Services : Senior Appointments

FRENCH HOSPITAL AND DISPENSARY, Shaftesbury-avenue, London, W.C.2. Applications invited for post of HONORARY DERMATOLOGIST. Candidates should be Fellows or Members of the Royal College of Physicians.

Applications (3 copies), with names of 2 referees, should be sent to the Secretary of the Hospital by 5th November, 1957.

ROYAL MASONIC HOSPITAL, Ravenscourt Park, London, W.6. Applications are invited from Fellows of one of the Royal Colleges of Surgeons for the appointment of CONSULTANT THORACIC SURGEON at the above Hospital as from on or about 1st January, 1958. Candidates must be engaged in consulting practice and well established in their profession.

Applications, giving detailed information and the names and addresses of 3 referees, should reach the undersigned (from whom further information may be obtained) on or before 12th October, 1957. R. E. LAWSON, Secretary and House Governor.

SOUTH EAST METROPOLITAN REGIONAL HOSPITAL BOARD. Applications are invited for an appointment as Part-time CONSULTANT in Diagnostic Radiology to undertake 9 notional half-days a week in the Woolwich Group of hospitals. Duties may include some sessions associated with the Regional Neurological/Neurosurgical and Thoracic Surgical Units at the Brook General Hospital. Candidates must have had a wide experience in the specialty and hold an appropriate diploma. The appointment will be in accordance with the terms and conditions of service of hospital medical and dental staffs (England and Wales). Candidates may visit the hospitals concerned.

Apply, stating nationality, age, sex, qualifications and experience, including details of present appointment and of war service, together with the names and addresses of 3 referees, to the Secretary, Advisory Appointments Committee, South East Metropolitan Regional Hospital Board, 11, Portland-place, W.1, not later than 12th October, 1957.

EXETER CLINICAL AREA. South-Western Regional HOSPITAL BOARD. Applications are invited for the appointment to the Exeter Clinical Area of a CONSULTANT PHYSICIAN with an interest in Geriatrics. The appointment may be held either on a whole-time or maximum (9 sessions) part-time basis. The successful candidate will have charge of general medical beds at the Royal Devon and Exeter Hospital, Exeter, Exeter City Hospital, and Tiverton District Hospital, and of geriatric beds at the Exeter City Hospital; he will also be required to visit other hospitals in the Clinical Area as determined by the Regional Hospital Board. Further particulars of the appointment can be forwarded upon request.

Applications (14 copies), stating date of birth, qualifications, and experience, together with the names and addresses of 2 referees, should be sent to the Secretary of the Regional Hospital Board, 27, Tyndalls Park-road, Bristol, 8, not later than 19th October, 1957.

LEEDS REGIONAL HOSPITAL BOARD. Consultant in Orthopædic Surgery (maximum part-time sessions). Duties at hospitals in the Hull A and East Riding Groups (mainly at Hull Royal Infirmary). 2 hours per week devoted to School Clinic Work. Person appointed to reside in Hull.

Applications (12 copies), stating age, qualifications and details of present and previous appointments with dates, and names and addresses of 3 referees, to the Secretary, Park-parade, Harrogate, by 21st October, 1957.

LIVERPOOL REGIONAL HOSPITAL BOARD. South LIVERPOOL GROUP. Applications are invited for the post of Whole-time ASSISTANT RADIOLOGIST (Senior Hospital Medical Officer) with duties in the above Group but mainly at Sefton General Hospital (816 Beds). Applicants should possess a Diploma in Radiology and have wide experience in radiology.

Forms of application from Dr. T. Lloyd Hughes, Senior Administrative Medical Officer, Liverpool Regional Hospital Board, 19, James-street, Liverpool, 2, to be returned not later than 19th October, 1957.

VINCENT COLLINGE, Secretary to the Board.

MANCHESTER REGIONAL HOSPITAL BOARD. Bury AND ROSSENDALE AND ROCHDALE AND DISTRICT HOSPITAL MANAGEMENT COMMITTEES. Locum CONSULTANT RADIOLOGIST (maximum part-time) required immediately for the above Hospital Centres, for approximately 2 months. Salary according to individual status.

Apply, stating full details to—

H. WILKINSON, Group Secretary.

Bury General Hospital, Bury, Lancs.

NEWCASTLE REGIONAL HOSPITAL BOARD. Assistant PSYCHIATRIST (Senior Hospital Medical Officer), whole-time at Winterton Hospital, Sedgefield (2000 Beds). Candidates should normally hold a D.P.M. but applications will be considered from candidates with no previous practical experience in psychiatry who hold a higher qualification, have had wide experience in general medicine, including Senior Registrar posts, and intend to obtain a D.P.M. and specialise in psychiatry. The appointment is resident, a suitable house is available. Further particulars from Regional Psychiatrist.

Applications, together with names and addresses of 3 referees to the Regional Psychiatrist, Newcastle Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 28 days.

NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD.

(1) CONSULTANT PSYCHIATRIST (whole-time), St. Bernard's Hospital, Southall, Middlesex (2507 Beds). Accommodation available for single candidate.

Applications before 21st October, 1957.

(2) CONSULTANT PSYCHIATRIST (whole-time), Hill End Hospital, St. Albans, Herts (692 Beds).

Applications before 24th October, 1957.

Hospitals may be visited by direct appointment.

Application forms obtainable from, and returnable to, Secretary, North West Metropolitan Regional Hospital Board, 11A, Portland-place, W.1.

SCOTLAND. WESTERN REGIONAL HOSPITAL BOARD. Applications are invited for the following appointments:

CONSULTANT PHYSICIAN at the Western Infirmary, Glasgow. The appointment is part-time on the basis of 8 notional half-days per week.

Whole-time ASSISTANT PSYCHIATRIST at Bellsdyke Mental Hospital, Larbert, and associated clinics. House available. Salary (at age 32 and over) on the scale £1653 15s.–£52 10s.–£2126 5s.

Applications (16 copies), stating date of birth, qualifications, experience, present appointment, and the names of 3 referees, to reach the Secretary, Western Regional Hospital Board, 64, West Regent-street, Glasgow, C.2, not later than 30 days after the publication of this advertisement.

SHEFFIELD REGIONAL HOSPITAL BOARD. Maximum Part-time CONSULTANT GENERAL SURGEON required. Duties in hospitals in the Leicester Area.

Application forms and further details from Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Sheffield, 10. Forms to be returned by 19th October, 1957.

SHEFFIELD REGIONAL HOSPITAL BOARD. Maximum Part-time CONSULTANT RADIOLOGIST required. Duties mainly in hospitals in the Mansfield Area.

Application forms and further details from Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield. Forms to be returned by 19th October, 1957.

SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time ASSISTANT ORTHOPÆDIC SURGEON required for Bretby Hall Orthopædic Hospital and associated clinics. Salary scale £1653 15s.–£52 10s.–£2126 5s.

Application forms and further details from Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield. Forms to be returned by 26th October, 1957.

SOUTH EAST METROPOLITAN REGIONAL HOSPITAL BOARD. Applications are invited for an appointment as Part-time CONSULTANT OBSTETRICIAN AND GYNÆCOLOGIST for 9 notional half-days a week in the Canterbury and Isle of Thanet Groups of hospitals. Candidates must have had wide experience in obstetrics and gynæcology and be Members of the Royal College of Obstetricians and Gynæcologists. The possession of other higher qualifications is desirable. The appointment will be in accordance with the terms and conditions of service of hospital medical and dental staffs (England and Wales). Candidates may visit the hospitals concerned.

Apply, stating nationality, age, qualifications and experience, including details of present appointment and war service, together with the names and addresses of 3 referees, to the Secretary, Advisory Appointments Committee, South East Metropolitan Regional Hospital Board, 11, Portland-place, London, W.1, not later than 12th October, 1957.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD. TONE VALE HOSPITAL, near TAUNTON. Applications are invited for the whole-time appointment of CONSULTANT PSYCHIATRIST to the South Somerset Clinical Area. Applicants should possess a higher qualification in Medicine and the D.P.M. Experience with electro-encephalography is desirable. The successful candidate, whose work will be mainly at Tone Vale Hospital and determined by the Medical Superintendent, will also be required to visit other hospitals in the Clinical Area as determined by the Regional Board.

Applications (12 copies), stating date of birth, qualifications, and experience, together with the names and addresses of 2 referees, should be sent to the Secretary of the Regional Hospital Board, 27, Tyndalls Park-road, Bristol, 8, not later than 19th October, 1957.

WELSH REGIONAL HOSPITAL BOARD. Whole-time ASSISTANT PSYCHIATRIST (Senior Hospital Medical Officer) North Wales Hospital for Nervous and Mental Disorders, Denbigh. Hospital provides comprehensive Mental Health Service for North Wales. Outpatient clinics at major general hospitals and associated child guidance services. Every modern therapy and Departments of Psychology and Electro-encephalography. Modern open-door reception units with annual admission rate of over 800. A house or flat suitable for a married man available.

Applications (12 copies), naming 3 referees, to Senior Administrative Medical Officer, Temple of Peace, Cathays Park, Cardiff, within 21 days.

OXFORD REGIONAL HOSPITAL BOARD. Consultant in Anæsthetics (whole-time or maximum part-time) to the hospitals of the Reading Hospital Management Committee. Applicants must hold the F.F.A.R.C.S. and have had wide experience in anæsthetics. The successful candidate will be required to live in the Reading area. Applicants may visit the hospitals by arrangement with the Hospital Management Committee Secretary.

Applications (9 copies), stating age, qualifications, experience, and the names of 3 referees, must reach the Secretary of the Board, 43, Banbury-road, Oxford, by 22nd October.

U.S.A. VIRGINIA. Progressive State mental hospital in Virginia, 4600 Beds, expanding staff, invites applications for PHYSICIANS at all levels, psychiatric experience desirable but not necessary. Salary from $5040 (approximately £2750). All modern methods of treatments. Opportunities for research. Good retirement plan.

Apply to JUUL C. NIELSEN, M.D., Superintendent, sending full résumé in first letter to Box 271, Petersburg, Virginia, U.S.A.

Hospital Services: Junior Appointments

BRITISH HOSPITAL FOR MOTHERS AND BABIES, Samuel-street, Woolwich, S.E.18. OBSTETRICAL HOUSE OFFICER, vacant 2nd November. Recognised for D.Obst. R.C.O.G. and M.R.C.O.G. approved for Pre-registration Service.

Apply to Group Secretary, Memorial Hospital, Woolwich, S.E.18.

BROMPTON HOSPITAL, S.W.3. Applications invited for the post of NON-RESIDENT HOUSE PHYSICIAN for which there are 2 vacancies for 6 months from 1st December, 1957. Duties include work in Outpatient Department and wards. Salary at the rate of £557 10s. p.a.

Applications, stating age, qualifications with dates, nationality, and appointments held, together with copies of testimonials, by 5th October, 1957, to—

KENNETH A. F. MILES, House Governor.

CENTRAL MIDDLESEX HOSPITAL, Park Royal, N.W.10. RESIDENT HOUSE OFFICER required in Surgical Department (post- or pre-registration). Post vacant 1st November, 1957.

Applications, with copies of 2 testimonials, to Medical Director by 5th October, 1957.

CONNAUGHT HOSPITAL, Walthamstow, E.17. (123 Beds.) Applications are invited for the post of SECOND CASUALTY OFFICER with duties in the Department of Orthopædic and Traumatic Surgery (Senior House Officer grade). Recognised for F.R.C.S. Salary £819 10s. p.a., less £150 p.a. for board, lodging, &c.

Applications, with full details and copies of 2 recent testimonials, should be sent immediately to Secretary, Forest Group Hospital Management Committee, Langthorne-road, E.11.

HACKNEY HOSPITAL, London, E.9. (General—341 Beds.) Applications for the 6 months Resident House Officer appointments of :—

(*a*) CASUALTY OFFICER AND HOUSE SURGEON (E.N.T.), now vacant.

(*b*) CASUALTY OFFICER AND HOUSE PHYSICIAN (Skin Department), now vacant.

Applications should be sent immediately to Secretary, above address, quoting C.O. (*a*) or (*b*).

HIGHLANDS GENERAL HOSPITAL, Winchmore Hill, N.21. SENIOR HOUSE OFFICER (medical) resident for Chest Unit (100 Beds). Duties include tuberculosis work and investigation and treatment of chest diseases under supervision of the Finchley Chest Clinic. Also general medical and geriatric work.

Applications, with copies of 3 testimonials, to Hospital Secretary.

LONDON CHEST HOSPITAL. Hospitals for Diseases OF THE CHEST. Applications are invited for the appointment of RESIDENT MEDICAL OFFICER. Appointment for 1 year from 1st December, 1957, and graded as Registrar.

Applications, stating date of birth, qualifications with dates, and previous appointments held, with copies of 3 testimonials, should be sent to the undersigned not later than 12th October.

THOMAS BROWN, House Governor.

London Chest Hospital, E.2.

METROPOLITAN HOSPITAL, Kingsland-road, London, E.8. Applications are invited from registered medical practitioners for the post of RESIDENT SENIOR HOUSE OFFICER (casualty), vacant 18th October, 1957. Post is recognised for F.R.C.S.

Applications, stating age, nationality, qualifications and experience, together with 3 testimonials, to the Hospital Secretary.

MIDDLESEX HOSPITAL, W.1. Applications invited for post of SENIOR REGISTRAR in Anæsthetics, vacant 1st January.

Rules and application forms obtainable from Deputy Superintendent should be returned, naming 2 referees, by 17th October.

NATIONAL HEART HOSPITAL, Maids Moreton, Buckingham. (Country Branch of the National Heart Hospital.) Applications are invited for the post of RESIDENT MEDICAL OFFICER at the Hospital's Country Branch. The appointment is for a period of 6 months from 1st November, 1957, but may be renewed for a further period not exceeding 6 months. The status of the post is that of a Senior House Officer and the salary is in accordance with the terms and conditions of service. The holder will be expected to attend on 1 day weekly at the Hospital in Westmoreland-street.

Applications, with copies of 3 recent testimonials, should be sent to me at Westmoreland-street, London, W.1, not later than 5th October, 1957.

ROBERT G. E. WHITNEY, Secretary to the Board.

NATIONAL HOSPITALS FOR NERVOUS DISEASES. Applications are invited from registered medical practitioners for the appointment of REGISTRAR (whole-time) to the Lysholm X-ray Department at The National Hospital, Queen-square, W.C.1. This post carries the grade of Registrar. Applicants should hold a Diploma in Diagnostic Radiology and have had experience in general radiology. The appointment will be for 6 months in the first instance.

Applications, with names of 3 referees, to be sent to the undersigned not later than 28th October, 1957.

H. EWART MITCHELL, Secretary to the Board of Governors.
The National Hospitals for Nervous Diseases,
Queen-square, London, W.C.1.

NATIONAL HOSPITALS FOR NERVOUS DISEASES. Applications are invited from registered medical practitioners for the appointment of REGISTRAR (non-resident) at The National Hospital, Queen-square, W.C.1. This post carries the grade of Senior Registrar. Previous neurological experience and higher medical qualification are desirable. The appointment will be for 1 year in the first instance.

Applications, with names of 3 referees, to be sent to the undersigned not later than 28th October, 1957.

H. EWART MITCHELL, Secretary to the Board of Governors.
The National Hospitals for Nervous Diseases,
Queen-square, London, W.C.1.

NORTH MIDDLESEX HOSPITAL, Edmonton, N.18. RESIDENT HOUSE SURGEON (general, orthopædic and traumatic surgery), pre- or post-registration, required for 6 months, starting 1st November. Post recognised for F.R.C.S.

Applications, stating age, nationality, qualifications, experience, with copies of recent testimonials, to Secretary of Hospital, by 2nd October.

QUEEN ELIZABETH HOSPITAL FOR CHILDREN MANAGEMENT COMMITTEE, Hackney-road, E.2, Shadwell, E.1, BANSTEAD, SURREY. HOUSE OFFICERS (2) commencing 1st December, 1957. 1 appointment will be made for 2 consecutive periods of 6 months. First period as House Physician at Shadwell, second as House Surgeon at Banstead (3 months) and Casualty Officer at Hackney-road (3 months). The second appointment is for the same rotation of duties but all at Hackney-road.

Application forms may be obtained from the Secretary at Hackney-road, and should be returned with copies of not more than 3 testimonials on or before 14th October, 1957.

QUEEN MARY'S HOSPITAL FOR THE EAST END, Stratford, E.15. JUNIOR CASUALTY OFFICER (House Officer third post) required for 6 months as soon as possible.

Applications, with the names of 3 referees, to the Hospital Secretary by 4th October, 1957.

ROYAL FREE HOSPITAL GROUP. Applications are invited for the post of SENIOR RESIDENT ANÆSTHETIST. Applicants must be registered medical practitioners. The appointment is for 6 months, to commence as soon as possible, with duties at the North Western Branch and Hampstead General Hospital. Salary in accordance with the Ministry of Health scale for Senior House Officers.

Application forms may be obtained from the Secretary, Royal Free Hospital, Gray's Inn-road, W.C.1, to whom they should be returned not later than 12th October, 1957.

ROYAL FREE HOSPITAL, London, W.C.1. Applications are invited from registered medical practitioners for the post of Whole-time NON-RESIDENT SENIOR REGISTRAR in Bacteriology. Appointment for 1 year in the first instance, beginning on or about 1st January, 1958. Experience in bacteriology and training in clinical pathology is essential.

Applications, together with the names of 3 referees, should be sent to the Secretary to the Board of Governors, at the above address, not later than 30th November, 1957.

ROYAL NATIONAL ORTHOPÆDIC HOSPITAL, BROCKLEY HILL, STANMORE, MIDDLESEX. Applications are invited for the post of RESIDENT SENIOR HOUSE OFFICER (2 vacancies) for a period of 6 months. Duties to commence on 30th November and 11th December, 1957.

Applications to be received by 14th October, 1957. Forms of application can be obtained from the House Governor at 234, Great Portland-street, London, W.1.

ROYAL NORTHERN HOSPITAL, N.7, AND PRINCE OF WALES'S HOSPITAL, Tottenham. SENIOR HOUSE OFFICER (Trainee) for Radiotherapy Departments at above Hospitals which can be visited by appointment.

Applications, with copies of recent testimonials, to be sent to Hospital Secretary, Royal Northern Hospital, N.7, by 8th October.

ROYAL NORTHERN HOSPITAL, Holloway-road, London, N.7. CLINICAL ASSISTANT (part-time) required for Dental Department. General Practitioner grade. 4 sessions per week.

Application forms and further particulars from Hospital Secretary.

SOUTH-EAST REGIONAL THORACIC SURGERY UNIT. (50 Beds.) BROOK GENERAL HOSPITAL, Shooters Hill-road, S.E.18. SENIOR HOUSE OFFICER, vacant 1st November. Recognised for F.R.C.S. 6 months appointment and may then be renewed for a further period. The Unit treats all types of chest diseases and offers opportunity for comprehensive training in thoracic surgery.

Apply to Group Secretary, Memorial Hospital, Woolwich, S.E.18.

THE HOSPITAL FOR SICK CHILDREN, Great Ormond-street, London, W.C.1. There will be a vacancy for a HOUSE PHYSICIAN (Senior House Officer) on 15th December, 1957.

Further particulars and form of application, which must be returned not later than 14th October, 1957, may be obtained from the undersigned.

H. F. RUTHERFORD, House Governor and Secretary.

ST. MARK'S HOSPITAL, City-road, London, E.C.1. Applications invited from Senior Registrars who have completed their training, or Registrars who have completed their appointment, for the post of RESIDENT SURGICAL OFFICER. Part of time non-resident by arrangement. Salary at the rate of £1540 or £1061 10s. respectively. Appointment tenable for 6 months from 1st December with possibility further extension 6 months.

Applications, stating age, qualifications, experience, names of 2 referees, to Secretary, Board of Governors, The Hammersmith, West London and St. Mark's Hospitals, Ducane-road, London, W.12, by 9th October.

ST. MARY'S HOSPITAL, Paddington, W.2. Senior REGISTRAR to the E.N.T. Department of St. Mary's Hospital required. Possession of a higher surgical qualification essential. The appointment will be for a first period of 12 months, as from a date to be arranged, and the successful candidate will be eligible for re-election.

Applications, stating nationality, date of birth, permanent address, qualifications with dates and details of previous appointments with gradings, together with the names and addresses of 3 referees, should reach ALAN POWDITCH, House Governor, not later than 15th October, 1957.

ST. PETER'S, ST. PAUL'S AND ST. PHILIP'S HOSPITALS. RESIDENT SURGICAL OFFICER (Senior Registrar grade), required for St. Paul's Hospital on 1st December, 1957. Applications invited from Male candidates on the British register who have completed their training in general surgery. Appointment for 6 months, with opportunity for a further 6 months if recommended. Candidate should be prepared to spend 1 year at the Hospital if required.

Applications (12 copies), and the names of 3 referees, should reach the House Governor, St. Peter's Hospital, Henrietta-street, W.C.2, by 31st October, 1957.

WEST LONDON HOSPITAL, Hammersmith-road, London, W.6. 2 RESIDENT HOUSE PHYSICIANS (general medicine) required; one 1st November, one 9th November. Pre-registration candidates considered.

Applications, stating age, qualifications, experience, copies of 2 recent testimonials, to Secretary by 7th October.

ALEXANDRIA, DUNBARTONSHIRE. VALE OF LEVEN HOSPITAL. (155 Beds.) Applications are invited for the post of RESIDENT HOUSE PHYSICIAN at the Vale of Leven Hospital for the current period. The post is recognised for pre-registration purposes.

Applications should be addressed to the Medical Superintendent at the above address.

ASHINGTON HOSPITAL. (52 Beds.) Wansbeck Hospital MANAGEMENT COMMITTEE. HOUSE OFFICER required immediately, also Locum for RESIDENT SURGICAL OFFICER (Junior Hospital Medical Officer). Some medical work will need to be undertaken by the House Officer.

Applications, with full details, &c., should be forwarded as early as possible to the Group Secretary, Wansbeck Hospital Management Committee, 12, Stanley-street, Blyth, Northumberland.

ASHTON, HYDE AND GLOSSOP HOSPITAL MANAGEMENT COMMITTEE. E.N.T. SURGEON (Senior House Officer grade) required at Ashton-under-Lyne General Hospital. Vacant early October.

Applications, stating age, qualifications and experience with copies of 2 testimonials, to be forwarded to the Group Secretary, General Hospital, Ashton-under-Lyne, Lancs, as soon as possible.

BARNSLEY. ST. HELEN HOSPITAL. (229 Beds. Recognised for M.R.C.O.G. and D.Obst. R.C.O.G.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT REGISTRAR (obstetrics and gynæcology) required immediately. Married accommodation available. There are 67 lying-in and ante-natal and 20 gynecological beds at this Hospital. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 7th October, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

BARNSLEY CHEST SERVICE. Sheffield Regional HOSPITAL BOARD. Whole-time REGISTRAR (chest diseases) required. Single accommodation available at Wathwood Hospital. Duties at the Hospital and Barnsley Clinics under the supervision of the Consultant. Appointment for 1 year in the first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 7th October, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

BARNSTAPLE. NORTH DEVON INFIRMARY. (105 Beds.) HOUSE SURGEON required; recognised pre-registration appointment.

Applications to Group Secretary, 19, Alexandra-road, Barnstaple.

BENENDEN CHEST HOSPITAL (Civil Service Sanatorium Society), BENENDEN, near CRANBROOK, KENT. (169 Beds.) SENIOR HOUSE OFFICER (resident) required, Male or Female, registered medical practitioner. Salary £715 p.a., plus untaxed free board and lodgings; transferable superannuation scheme. The Hospital, which is independent of the National Health Service, is fully equipped for the treatment, including regular major thoracic surgery, of adult male and female patients with pulmonary disease, tuberculous and non-tuberculous.

Applications, stating age, qualifications, experience, with names of 2 referees, should be sent to the Chief Medical Officer as soon as possible.

BEVERLEY, YORKSHIRE. WESTWOOD HOSPITAL. ASSISTANT PATHOLOGIST (Senior House Officer grade) required for Area Laboratory. Offers experience in all branches of pathology.

Detailed applications to Group Secretary.

BEVERLEY, YORKSHIRE. WESTWOOD HOSPITAL. (229 acute beds.) ORTHOPÆDIC HOUSE SURGEON (first, second or third post), vacant now. Offers good opportunity for general experience in busy acute general hospital. Approved pre-registration post. Fully qualified practitioners may apply. Recognised for F.R.C.S.

Apply Group Secretary.

BEVERLEY, YORKSHIRE. WESTWOOD HOSPITAL. (229 Beds.) HOUSE PHYSICIAN (House Officer or Senior House Officer grading according to experience).

Apply Group Secretary.

BEDFORD GENERAL HOSPITAL, Bedford. (436 Beds.) NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. MEDICAL REGISTRAR, vacant mid-October; appointment for 1 year, renewable for second year. Hospital may be visited by writing to Senior Physician.

Application forms obtainable from, and returnable to, Group Secretary, Bedford Group Hospital Management Committee, 3, Kimbolton-road, Bedford.

BIRMINGHAM AND MIDLAND EYE HOSPITAL, Church-street, BIRMINGHAM, 3. (156 Beds.) HOUSE OFFICER (resident) required. Previous ophthalmic experience essential. Recognised for D.O. and F.R.C.S. in ophthalmology. Wide experience available in all branches including surgery.

Detailed applications to the Group Secretary, Dudley Road Hospital, Birmingham, 18.

BIRMINGHAM, 9. LITTLE BROMWICH GENERAL HOSPITAL. PÆDIATRIC HOUSE PHYSICIAN (Male or Female). Post vacant 23rd October, 1957. Recognised for D.C.H. Includes duties on infectious diseases ward, Neonatal Department and clinic.

Apply Physician-Superintendent.

BIRMINGHAM, 18. DUDLEY ROAD HOSPITAL. (780 Beds.) HOUSE SURGEON required in Obstetrics and Gynæcological Department (vacant 1st November, 1957). Recognised for pre-registration and M.R.C.O.G. The Department under the direction of a Senior Consultant Obstetrician, consists of 115 maternity beds, 100 neonatal cots, and 60 gynæcological beds.

Detailed applications, with copies of 3 recent testimonials, to the Group Secretary.

BIRMINGHAM REGIONAL HOSPITAL BOARD.

(1) **Shrewsbury Group 15, Royal Salop Infirmary, Shrewsbury**

REGISTRAR (surgery). Duties mainly at Royal Salop Infirmary and Copthorne Hospital (170 surgical beds). Experience in specialty essential. Higher qualification desirable. Hospital recognised for F.R.C.S. Resident or non-resident.

(2) **Birmingham (Dudley Road) Group, Dudley Road Hospital, Birmingham, 18**

(*a*) REGISTRAR (surgical), Dudley Road Hospital. Considerable experience essential—high qualifications an advantage. Excellent opportunities for wide range of experience.

(*b*) REGISTRAR (E.N.T. surgery), non-resident. Dudley Road Hospital (approximately 40 E.N.T. beds). Post recognised for D.L.O. Experience specialty and higher qualifications an advantage.

Application forms from Group Secretaries to be returned by 7th October, 1957.

BIRMINGHAM. THE UNITED BIRMINGHAM HOSPITALS. QUEEN ELIZABETH HOSPITAL. Applications are invited for the post of MEDICAL REGISTRAR (Registrar grade). The post is tenable for 1 year in the first instance. Candidates should have the M.R.C.P. (London). The successful candidate will be required to take part in resident duties.

Forms of application may be obtained from, and should be returned not later than 19th October, 1957, to, the Secretary, The United Birmingham Hospitals, Queen Elizabeth Hospital, Birmingham, 15.

BIRMINGHAM. THE UNITED BIRMINGHAM HOSPITALS. Applications are invited for the appointment of SURGICAL REGISTRAR (Registrar grade) to the Surgical Professorial Unit, United Birmingham Hospitals. Candidates must have held a resident appointment and should have the F.R.C.S. The successful candidate will be required to take part in a rota of resident duties.

Forms of application from the Secretary, United Birmingham Hospitals, Queen Elizabeth Hospital, Birmingham, 15, to be returned by 19th October, 1957.

BISHOP'S STORTFORD, HERTFORDSHIRE. HERTS AND ESSEX GENERAL HOSPITAL. (386 Beds.) SENIOR HOUSE OFFICER (surgical) required for general and orthopædic surgical duties. Salary £819 10s. p.a., less £150 in respect of residential emoluments.

Further particulars from, or applications with names of 2 referees to, the Hospital Secretary.

BISHOP'S STORTFORD, HERTFORDSHIRE. HERTS AND ESSEX GENERAL HOSPITAL. (386 Beds.) Applications are invited for the post of HOUSE OFFICER (surgical), pre-registration. Salary £467 10s.–£522 10s. p.a., less £125 in respect of residential emoluments. Appointment to commence immediately. There is a pre-registration medical post for which the successful candidate will receive consideration at the termination of the surgical appointment.

Applications, stating age, nationality, qualifications, and experience, with copies of 2 recent testimonials or the names of referees, to the Hospital Secretary.

BOURNEMOUTH (near). CHRISTCHURCH HOSPITAL, CHRISTCHURCH, HANTS. BOURNEMOUTH AND EAST DORSET HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the appointment of a RESIDENT SENIOR HOUSE OFFICER, (surgical) for the above Hospital of 334 Beds, including a new Surgical Unit of 56 Beds. The post became vacant on 1st September, 1957. There is no emergency surgery undertaken at the moment, but the successful applicant will attend surgical outpatient sessions at the Royal Victoria Hospital, Boscombe.

Applications to the Hospital Secretary, Christchurch Hospital.

BOLTON AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE.

The Royal Infirmary, Bolton (238 Beds)

SENIOR HOUSE OFFICER for Casualty Department with some orthopædic duties. Recognised for F.R.C.S. Resident or non-resident. Staff of two with Consultant supervision and adequate relief. Post offers good Casualty/Accident experience.

Bolton District General Hospital (Townleys Branch Psychiatric Unit)

SENIOR HOUSE OFFICER in Psychiatry (resident). Unit is attached to a General Hospital. Consultant Psychiatrist-in-charge. All forms of modern treatment in use. Post offers excellent facilities for anyone desiring to specialise in psychiatry and attend D.P.M. course at Manchester University. Hospital also recognised for London and Irish D.P.M. Outpatient clinics in existence. Vacant 8th October and tenable for 12 months.

Applications, stating age, nationality, qualifications, experience and the names of 2 referees, should be sent immediately to Group Secretary, The Royal Infirmary, Bolton.

BLACKBURN. ROYAL INFIRMARY. (262 general beds.) BLACKBURN AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. JUNIOR HOSPITAL MEDICAL OFFICERS or SENIOR HOUSE OFFICERS (casualty and orthopædics) (2) required 6th October and 26th October, 1957. Junior Hospital Medical Officer posts can be for any period up to 4 years. Recognised for F.R.C.S.

Apply to Group Secretary, Hospital Management Committee Office, Royal Infirmary, Blackburn.

BRIGHTON AND LEWES HOSPITAL MANAGEMENT COMMITTEE. NEW SUSSEX HOSPITAL FOR WOMEN AND SUSSEX MATERNITY HOSPITAL. OBSTETRIC AND GYNÆCOLOGICAL HOUSE SURGEON (Female). Obstetrics at Sussex Maternity (56 Beds) and Gynæcological Department (24 Beds) at New Sussex Hospital.

Applications, giving age, experience and names of 2 referees, to be sent to the Administrative Officer, New Sussex Hospital, Windlesham-road, as soon as possible.

BRIGHTON GENERAL HOSPITAL. Brighton and LEWES HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the position of HOUSE PHYSICIAN to the Geriatric Unit. This is a large Unit with an active rehabilitation section, which provides excellent clinical facilities. Vacant 1st November.

Applications, stating age, qualifications, and experience, together with copies of recent testimonials, should be sent to the Physician-Superintendent, Brighton General Hospital, Elmgrove, Brighton, 7.

BRIGHTON. ROYAL SUSSEX COUNTY HOSPITAL. (312 Beds.) HOUSE SURGEON required end October. Pre-registration and recognised for F.R.C.S.

Applications, stating usual particulars, and naming 2 referees, to the Administrative Officer, Royal Sussex County Hospital, Brighton, 7.

BRISTOL. COSSHAM AND FRENCHAY HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER required for the Department of Thoracic Surgery (120 Beds) at Frenchay Hospital.

Apply to Group Secretary, Frenchay Hospital, Bristol, giving age and experience and quoting 2 referees.

BURTON-ON-TRENT. THE GENERAL HOSPITAL. HOUSE SURGEON (general and pre-registration) required immediately at the above Hospital. Post recognised for F.R.C.S.

Applications to Group Secretary as soon as possible.

BUXTON. DEVONSHIRE ROYAL HOSPITAL. (252 Beds.) Applications are invited for the post of RESIDENT SENIOR HOUSE OFFICER. This Hospital is a large special hospital for the treatment and rehabilitation of all types of locomotor disorders. Duties are mainly medical and include work in the long-stay unit of the Manchester University Rheumatism Research Centre. The Hospital is recognised under the regulations for the Diploma in Physical Medicine, Part II, and the post also offers good medical experience.

Applications, stating age, experience and qualifications, together with the names of 2 persons for reference, to be addressed to the Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport, immediately.

CAERNARVON AND ANGLESEY HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for HOUSE SURGEONS at each of the following hospitals :—

LLANDUDNO GENERAL HOSPITAL, LLANDUDNO. (Recognised for F.R.C.S.)

CAERNARVON AND ANGLESEY GENERAL HOSPITAL, BANGOR. (Recognised for F.R.C.S.)

The appointments are for a period of 6 months. Salary and conditions of service in accordance with those approved by the Ministry of Health.

Applications, stating age, qualifications and experience, together with the names and addresses of 2 referees, to be forwarded to the Group Secretary, Plas Gwyn, Ffriddoedd-road, Bangor, within 10 days of the appearance of this advertisement.

CAERPHILLY HOSPITAL. (226 Beds for acute general medicine and surgery.) Pre-registration HOUSE OFFICER (orthopædics and general surgery) required at above Hospital.

Apply immediately, with names of referees, to the Group Secretary, Rhymney and Sirhowy Valleys Hospital Management Committee, Central Offices, Caerphilly-road, Ystrad Mynach, Glam.

CARDIFF. THE UNITED CARDIFF HOSPITALS. Applications are invited for the appointment of REGISTRAR to the Orthopædics and Fracture Departments, to commence duty as soon as possible.

Application forms are available from the Secretary to the Board, at the Cardiff Royal Infirmary, Newport-road, Cardiff, and should be returned within 14 days of the appearance of this advertisement.

CARDIFF (near). PRINCE OF WALES ORTHOPÆDIC HOSPITAL, RHYDLAFAR, near CARDIFF. SENIOR HOUSE OFFICER required. Regional Orthopædic Centre for South Wales area. 281 Beds and branch hospital of 70 Beds. Outpatient clinic in Cardiff. Full staff of Consultants and Registrars. Single accommodation available at Hospital at Rhydlafar.

Form of application from Group Secretary, 44, Cathedral-road, Cardiff.

CARDIFF. ST. DAVID'S HOSPITAL. Resident Obstetrical HOUSE OFFICER (recognised for M.R.C.O.G.) required in Maternity Department at above Hospital, commencing 1st November, 1957.

Form of application from Group Secretary, Cardiff Hospital Management Committee, 44, Cathedral-road, Cardiff.

CARDIFF. ST. DAVID'S HOSPITAL. Senior House OFFICER required for Accident Unit at above Hospital.

Form of application from Group Secretary, Cardiff Hospital Management Committee, 44, Cathedral-road, Cardiff.

CARMARTHEN. WEST WALES GENERAL HOSPITAL. (188 Beds.) WEST WALES HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of SENIOR HOUSE OFFICER (orthopædic and traumatic surgery) (recognised by the Royal College of Surgeons), which will become vacant early in October. Salary and conditions of service as laid down by the Ministry of Health.

Applications, stating age, qualifications, experience, nationality, and names and addresses of 3 referees, to the Group Secretary, West Wales Hospital Management Committee, Glangwili, Carmarthen.

CHELMSFORD. ST. JOHNS' HOSPITAL. (Recognised for M.R.C.O.G.) RESIDENT GYNÆCOLOGICAL HOUSE SURGEON to commence as soon as possible. Preference will be given to candidates who intend to obtain the Diploma of Membership of the Royal College of Gynæcologists.

Applications, stating age, nationality, qualifications and experience, together with recent testimonials, should be sent immediately to the Secretary, Chelmsford Group Hospital Management Committee, Chelmsford and Essex Hospital, London-road, Chelmsford.

CHESTERFIELD HOSPITAL MANAGEMENT COMMITTEE. JUNIOR HOSPITAL MEDICAL OFFICER required 14th October at Whittington Hall, Chesterfield (356 Beds for female mentally deficient patients), and Scarsdale Hospital, Chesterfield, where there are 125 Beds for mental patients. Previous experience in psychiatry not essential. Ample opportunities for study. Flat available within the Group.

Apply, with names of 3 referees, to Group Secretary, The Royal Hospital, Chesterfield.

CHESTERFIELD. SCARSDALE HOSPITAL. Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER for Geriatric Unit and for duties at Penmore Hospital. Full Consultant services. Excellent scope for doctor interested in this specialty. House available on service tenancy.

Applications, giving full particulars, with names of 3 referees, to Group Secretary, Chesterfield Hospital Management Committee, at Chesterfield Royal Hospital.

CHICHESTER. ROYAL WEST SUSSEX HOSPITAL. (202 acute Beds.) RESIDENT HOUSE SURGEON required for 6 months appointment. National salary scale for either provisionally or full registered practitioners. Post approved for pre-registration practitioners and F.R.C.S. 8 residents. Vacant 13th October.

Applications, stating age, experience, qualifications, with references or names of referees, to Senior Administrative Officer.

COLCHESTER GROUP HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for :—

Essex County Hospital, Colchester, Essex (185 Beds)

Post of SENIOR HOUSE OFFICER to Casualty and E.N.T. Departments.

Post of SENIOR HOUSE OFFICER to Casualty and Radiotherapy Departments.

Posts tenable for 6 months or 1 year. Recognised for F.R.C.S.

Black Notley Hospital, Braintree, Essex (516 Beds)

Post of HOUSE OFFICER (orthopædic surgery). Duties include care of cases from London Hospital Orthopædic Department. First, second, third, or pre-registration post, tenable for 6 months. Recognised for F.R.C.S.

Applications, with copies of 3 testimonials, to Group Secretary, Colchester Hospital Management Committee, 14, Pope's-lane, Colchester, Essex.

DERBY. DERBYSHIRE ROYAL INFIRMARY. (416 Beds.) SENIOR HOUSE OFFICER (casualty), vacant 2nd November. Recognised for periods of 6 months casualty training for F.R.C.S. The staffing of the department is a Senior Casualty Officer and 2 Senior House Officers.

Apply, stating age, experience, and 2 names for reference, to Secretary.

DUDLEY, STOURBRIDGE AND DISTRICT HOSPITAL GROUP, BIRMINGHAM REGION.

The Guest Hospital, Dudley (154 Beds)

CLINICAL ASSISTANT in E.N.T. Surgery, to assist at Outpatient Department on Monday and Tuesday afternoons.

Applications, with references, to Group Secretary, Guest Hospital, Dudley.

HOUSE OFFICER (surgical), pre-registration. Post vacant 1st October, 1957.

Apply Group Secretary, Guest Hospital, Dudley, Worcs.

DURHAM. COUNTY HOSPITAL. (116 Beds.) Resident HOUSE SURGEON required in Orthopædics and Casualty. Post recognised for pre-registration purposes. This post offers facilities for good and varied experience in a busy orthopædic and accident hospital which serves a wide mining and industrial area.

Apply, giving age, experience and names of 2 referees, to the Group Secretary, Dryburn Hospital, Durham.

DURHAM. COUNTY HOSPITAL. (116 Beds.) Senior HOUSE OFFICER in Orthopædics required immediately. Resident. The County Hospital is the main Orthopædic and Accident Hospital in a busy mining and industrial area. Experience can be obtained in all branches of orthopædics.

Applications, with particulars of previous experience and names of 2 referees, to Group Secretary, Dryburn Hospital, Durham.

DONCASTER ROYAL INFIRMARY. (330 Beds.) Applications are invited for the post of HOUSE SURGEON (Intern or Senior House Officer). Post recognised for F.R.C.S.

Applications to the Group Secretary, Doncaster Hospital Management Committee, at Doncaster Royal Infirmary.

DONCASTER. WESTERN HOSPITAL. (178 Beds. Recognised for the D.Obst. R.C.O.G. and M.R.C.O.G.) SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time RESIDENT REGISTRAR (obstetrics and gynæcology) required 6th November. Appointment for 1 year in first instance.

Apply to Secretary, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, by 7th October, 1957, giving age, nationality, qualifications, present and previous appointments with dates, naming 3 referees.

DRIFFIELD, YORKSHIRE. EAST RIDING GENERAL HOSPITAL. (247 Beds.) HOUSE PHYSICIAN, approved pre-registration post. Fully qualified practitioners may apply. Duties include acute and chronic medicine. Good general experience for first house appointment.

Apply Group Secretary, Westwood Hospital, Beverley, Yorkshire.

EAST ANGLIAN REGIONAL HOSPITAL BOARD. RADIOLOGICAL REGISTRAR, West Suffolk Group of hospitals. Main hospital West Suffolk General, Bury St. Edmunds (262 Beds). Successful applicant will work directly under the Consultant Radiologist. Appointment for 1 year, renewable for second year.

Applications, stating age, experience and the names of 3 referees, to the Board's Senior Administrative Medical Officer, 117, Chesterton-road, Cambridge, by 7th October, 1957. Candidates are invited to visit, by direct arrangement with Hospital Management Committee Secretary, West Suffolk Hospital.

EDGWARE GENERAL HOSPITAL, Edgware, Middlesex. RESIDENT HOUSE SURGEON for above Hospital. Post vacant 13th October, 1957. 6 months appointment. Recognised for F.R.C.S. and pre-registration purposes.

Applications, stating age, qualifications, experience and enclosing copies of up to 3 recent testimonials, to Medical Director of Hospital by 11th October, 1957.

ENFIELD, MIDDLESEX. CHASE FARM HOSPITAL. Applications are invited for the post of RESIDENT PATHOLOGIST (Senior House Officer grade) for duties in the Area Laboratory and at other hospitals in the Group. The Area Laboratory is recognised for the Diploma of Pathology of the Royal Colleges of Physicians and Surgeons. Further information can be obtained from the Senior Pathologist. Appointment tenable for 1 year.

Applications, with the names of 2 referees, to the Group Secretary, Enfield Group Hospital Management Committee, at Chase Farm Hospital, by 12th October, 1957.

EXETER. ROYAL DEVON AND EXETER HOSPITAL. Applications are invited from pre-registration and registered medical practitioners for the posts of HOUSE SURGEON (general surgery) (2) vacant on 2nd November, 1957, and 9th November, 1957, respectively.

Applications, with copies of 2 recent testimonials, to the Hospital Secretary immediately.

GLASGOW. HAWKHEAD (MENTAL) HOSPITAL, 510, Crookston-road, GLASGOW, S.W.3. Applications are invited for the post of SENIOR HOUSE OFFICER in Psychiatry (Male or Female), resident or non-resident. The post offers wide experience and training in all aspects of psychiatry (in-patient and outpatient), and all modern methods of treatment are carried out. Recognised for D.P.M.

Applications, together with the names of 2 referees, should be forwarded as soon as possible to Physician-Superintendent at above address.

GLASGOW NORTHERN HOSPITALS BOARD OF MANAGEMENT. Applications are invited for 2 immediate vacancies for JUNIOR HOSPITAL MEDICAL OFFICERS in the Infectious Diseases Department (450 Beds). Excellent experience in infectious diseases and general medicine. Undergraduate and postgraduate teaching unit and Regional centre for treatment of poliomyelitis.

Applications, stating age, nationality, qualifications, and experience with names of 2 referees, to Physician-Superintendent, Ruchill Hospital, Glasgow, N.W.

GLASGOW NORTHERN HOSPITALS BOARD OF MANAGEMENT. Applications are invited for 2 immediate vacancies for JUNIOR HOSPITAL MEDICAL OFFICERS, Ruchill Hospital, Glasgow, N.W., in the Chest Department (Medical Unit). The department consists of 200 Beds for the treatment of pulmonary tuberculosis and other diseases of the chest. There is attached to the department a Thoracic Surgical Unit of 60 Beds. Facilities are available for postgraduate study and research.

Applications, stating age, nationality, qualifications, and experience, with names of 2 referees, to Physician-Superintendent immediately.

GLASGOW. VICTORIA INFIRMARY. Applications are invited for the post of SENIOR HOUSE OFFICER in Orthopædics for duties at the Victoria Infirmary, Glasgow, and a large unit at the Victoria Auxiliary Infirmary, Philipshill. The post, which is tenable for 1 year, is resident at Philipshill.

Applications, with names of 2 referees, to the Secretary, Board of Management for Glasgow Victoria Hospitals, 24, St. Vincent-place, Glasgow, C.1.

GRIMSBY GENERAL HOSPITAL. Applications are invited for CASUALTY OFFICER (Senior House Officer grade) with some E.N.T. duties. Post vacant in November. Up-to-date Medical Library and reading facilities available.

Applications, with names and addresses of 2 referees, to Hospital Secretary.

HALIFAX. NORTHOWRAM HALL HOSPITAL. (108 Beds.) SENIOR HOUSE OFFICER in Chest Diseases required. Post vacant 1st October, 1957. Duties include attendance at busy Chest Clinic, at the Royal Halifax Infirmary, and non-tuberculosis chest ward work. This post offers excellent facilities for a study of chest diseases and experience is available with bronchoscopies and bronchograms. Salary £819 10s. p.a., with a deduction of £150 p.a. for board, residence, &c.

Applications to be forwarded to the Group Secretary, Royal Halifax Infirmary, Halifax.

HALIFAX. ST. JOHN'S HOSPITAL. (382 Beds.) Senior HOUSE OFFICER in Geriatrics and General Medicine required. Post vacant 16th October, 1957. Salary £819 10s. p.a., with deduction of £150 p.a. for board-residence, &c.

Applications to the Group Secretary, Royal Halifax Infirmary, Halifax.

HASTINGS. ROYAL EAST SUSSEX HOSPITAL. (150 Beds.) Locum SENIOR HOUSE OFFICER (casualty) required any 2 weeks in October. Rate of pay £15 19s. per week.

Apply immediately to Hospital Administrator.

HEREFORD. GENERAL HOSPITAL. (154 Beds.) HOUSE OFFICER (general surgery) required, pre-registration post. Hospital recognised by R.C.S. Duties include care of general surgical beds and in addition for 3 months of orthopædic beds and for 3 months of E.N.T. beds.

Applications, with copies of 2 testimonials, to be sent to the Group Secretary, Victoria House, Eign-street, Hereford.

HITCHIN. LISTER HOSPITAL. (330 Beds.) North West METROPOLITAN REGIONAL HOSPITAL BOARD. Whole-time MEDICAL REGISTRAR (resident) required at above Hospital. Post gives good all-round experience in general medicine and paediatrics, valuable for the M.R.C.P. Vacant 7th November, 1957. Hospital may be visited by direct appointment.

Application forms obtainable from, and returnable to, Secretary, Luton and Hitchin Group Hospital Management Committee, St. Mary's Hospital, Luton, Beds, by 7th October, 1957.

HOVE GENERAL HOSPITAL, Sussex. (75 Beds. 3 Resident Medical Officers.) Pre-registration HOUSE SURGEON (with casualty duties) required for period of 6 months. This post, which is now vacant is recognised for F.R.C.S., and provides a wide experience in an active surgical unit. Salary £467 10s.–£577 10s., less £125 p.a., for residential emoluments.

Applications, stating age, qualifications, full details of experience, together with names and addresses of 2 referees, to the Administrative Officer.

HULL. KINGSTON GENERAL HOSPITAL. (419 Beds.) HULL A GROUP HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON (pre-registration post), resident, and tenable for 6 months. This post includes gynæcology and general surgery.

Applications, with 2 recent testimonials, to the Hospital Secretary.

HUDDERSFIELD ROYAL INFIRMARY. (285 Beds.) HUDDERSFIELD HOSPITAL MANAGEMENT COMMITTEE. HOUSE SURGEON required to commence duty immediately. The post is recognised as a pre-registration appointment and for the F.R.C.S. Salary in accordance with national scale.

Applications, together with copies of 3 recent testimonials, to be addressed to the undersigned as soon as possible.

H. J. JOHNSON, Secretary to the Management Committee.

The Royal Infirmary, Huddersfield.

KENDAL. WESTMORLAND COUNTY HOSPITAL. JUNIOR HOSPITAL MEDICAL OFFICER (surgical) required in the Surgical Unit. The post offers excellent experience in general surgery. The successful candidate will also be expected to participate in the general work of the Hospital. Salary will be determined by applicant's present post and previous service.

Full particulars, stating age, experience and qualifications, with names of 2 referees, should be forwarded to the Group Secretary, Royal Lancaster Infirmary, Lancaster.

KETTERING GENERAL HOSPITAL, Kettering. (130 Beds.) KETTERING AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. Applications are invited from registered medical practitioners for the appointment of SENIOR HOUSE OFFICER in Anæsthetics. Post vacant now. Post recognised for D.A.

Applications, giving details of qualifications and experience, and enclosing copies of 3 recent testimonials, to be sent to the Group Secretary at the above address.

ILKLEY. MIDDLETON HOSPITAL. (430 Beds.) RESIDENT JUNIOR HOSPITAL MEDICAL OFFICER required at the above Hospital. This appointment provides for experience in the specialties of tuberculosis and geriatrics.

Applications, stating age, nationality, qualifications and experience, to Hospital Secretary.

IPSWICH. ST. HELEN'S HOSPITAL. (129 Beds for infectious diseases, pulmonary tuberculosis, long-stay orthopædics and geriatrics. The area Chest Clinic is in the Hospital.) HOUSE PHYSICIAN required (post-registration appointment). Accommodation available for married man.

Applications to JOHN WILLIAMS, Group Secretary, Ipswich Group Hospital Management Committee, at the Ipswich and East Suffolk Hospital (Anglesea Road Wing), Ipswich.

IPSWICH AND EAST SUFFOLK HOSPITAL. Anglesea ROAD WING. (356 Beds.) Applications are invited for the post of SENIOR HOUSE SURGEON to the Fracture and Orthopædic Department. The post is graded Senior House Officer and is recognised for the F.R.C.S. examinations. The Department has 2 Consultants, about 60 Beds and a large outpatient attendance; it offers wide experience.

Applications, stating age, nationality and experience, together with copies of recent testimonials, to the Hospital Secretary.

IPSWICH AND EAST SUFFOLK HOSPITAL, Heath ROAD WING, IPSWICH. (280 Beds.) Post of HOUSE PHYSICIAN (pre-registration) vacant 17th October, 1957.

Applications, stating qualifications, age, nationality, &c., with copies of 3 recent testimonials, to Hospital Secretary.

LANARK. BELLEFIELD SANATORIUM. Resident JUNIOR HOSPITAL MEDICAL OFFICER required for above Sanatorium.

Applications to the Secretary, Board of Management for Glasgow Victoria Hospitals, 24, St. Vincent-place, Glasgow, C.1.

LANCASTER. BEAUMONT HOSPITAL, Slyne-road. SENIOR HOUSE OFFICER (infectious diseases). Hospital recognised for D.C.H. and contains paediatric, dermatological, E.N.T., infectious diseases and pulmonary tuberculosis units. The duties are such as to suit a candidate reading for higher examinations.

Applications, together with names of 2 referees, to Group Secretary, Royal Lancaster Infirmary, Lancaster.

LEAMINGTON SPA. WARNEFORD GENERAL HOSPITAL. (197 Beds.) CASUALTY OFFICER (Senior House Officer), Male or Female, resident or non-resident. Post vacant 12th November, 1957, and suitable for one reading for higher qualifications being recognised for F.R.C.S., affording contact with all Specialist Units in the Hospital.

Applications, with names and addresses of 3 referees, to Hospital Secretary.

LEAMINGTON SPA. WARNEFORD GENERAL HOSPITAL. (197 Beds.) RESIDENT HOUSE SURGEON (general surgery). Post vacant 8th October, 1957. Recognised for pre-registration and F.R.C.S. Post provides excellent experience. Good accommodation available.

Applications, with 2 recent testimonials, to Hospital Secretary.

LEEDS REGIONAL HOSPITAL BOARD. Registrar vacancies.

Chest Diseases

Scotton Banks Sanatorium, Knaresborough (200 staffed beds). Visiting staff includes Teaching Hospital Consultants. Resident.

General Medicine

Applications are invited for the post of Research Registrar in Rheumatism to assist the Professor of Clinical Medicine with research projects at the Royal Bath Hospital, Harrogate, which is the centre for the Regional Rheumatism Scheme, or elsewhere in the Region. This appointment is associated with the University of Leeds.

Infectious Diseases

Leeds Road Hospital, Bradford (120 I.D. beds). Resident.

Applications, stating age, sex, qualifications, and details of present and previous appointments with dates, together with the names and addresses of 3 referees, to the Secretary to the Joint Registrars Committee, Park-parade, Harrogate, not later than 9th October, 1957.

LEEDS, 14. SEACROFT HOSPITAL. Leeds (Group B) HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER in Infectious Diseases. The Infectious Diseases Section, average bed occupancy 100, is an I.D. undergraduate and postgraduate training unit and a Regional Poliomyelitis Centre. Additional post for 6 months only.

Applications, giving personal particulars, qualifications and experience, with names of 3 referees, to Group Secretary, Seacroft Hospital, Leeds, 14.

LINCOLN. ST. GEORGE'S HOSPITAL. (242 Beds.) Applications are invited for the post of pre-registration HOUSE PHYSICIAN or SENIOR HOUSE OFFICER in General Medicine at the above Hospital which has been recently recommissioned.

Applications, giving full particulars, together with not less than 2 names for reference, should be forwarded to the Secretary as soon as possible.

LINCOLN. ST. GEORGE'S HOSPITAL, Long Leys-road. (242 Beds.) Applications are invited for the post of SENIOR HOUSE OFFICER in Gynæcology.

Applications, giving full particulars, together with not less than 2 names for reference, should be forwarded to the Secretary as soon as possible.

LIVERPOOL, 20. BOOTLE HOSPITAL. There will be a vacancy for a HOUSE PHYSICIAN from mid-October. Recognised for Pre-registration Service.

Apply to Secretary, Walton Hospital, Liverpool, 9, stating age, qualifications, experience, names of 2 referees, and date of availability for duty.

LIVERPOOL. THE UNITED LIVERPOOL HOSPITALS. Applications are invited for a post of REGISTRAR in Anæsthetics to take up duty as soon as possible for the period to 30th September, 1958. Annual reappointment thereafter until completion of the normal period of training will be considered without need for further application. Registrars in anæsthetics are required to spend 6 months in each 2 years at the Liverpool Maternity Hospital and while undertaking this duty they are required to be resident.

Apply by 11th October, 1957, on form obtainable from the Secretary, 80, Rodney-street, Liverpool, 1.

LUTON AND DUNSTABLE HOSPITAL, Luton, Bedfordshire. Locum SURGICAL REGISTRAR (resident) required for 4 weeks from 30th September to 27th October, 1957.

Applications, giving full particulars and names of referees, to Secretary, Luton and Dunstable Hospital, Luton, Beds.

LUTON AND DUNSTABLE HOSPITAL. North West METROPOLITAN REGIONAL HOSPITAL BOARD. ANÆSTHETIC REGISTRAR (resident or non-resident) required at the above Hospital (250 Beds) and associated units (134 Beds), for a 1-year or 2-year appointment. Post recognised for D.A. and F.F.A.R.C.S., and now vacant. The Hospital may be visited by direct appointment.

Application forms obtainable from the Secretary, Luton and Hitchin Group Hospital Management Committee, St. Mary's Hospital, Luton, and returnable as soon as possible.

MANCHESTER REGIONAL HOSPITAL BOARD. Applications are invited for the full-time post of ORTHOPÆDIC REGISTRAR in the Ashton, Hyde and Glossop Group of hospitals, with duties mainly at Ashton-under-Lyne General Hospital. There are approximately 40 orthopædic beds and busy Orthopædic and Casualty Outpatients Department. The post is recognised for additional training under F.R.C.S. regulations and is vacant on 1st November.

Applications, stating age, nationality, qualifications and experience, with copies of 2 references, should be forwarded to the Group Secretary, Ashton, Hyde and Glossop Hospital Management Committee, General Hospital, Ashton-under-Lyne, Lancashire, as soon as possible.

MANCHESTER REGIONAL HOSPITAL BOARD. South MANCHESTER HOSPITAL MANAGEMENT COMMITTEE. BAGULEY HOSPITAL. (402 Beds.) The Board invite applications for the post of REGISTRAR in Thoracic Surgery. This Hospital is a large Thoracic Unit fully equipped for the medical and surgical treatment of tuberculosis and other chest diseases. Attached to the Hospital is a chest clinic. The post offers opportunities for wide experience in medical and surgical treatment of patients suffering from tuberculosis and other diseases of the chest, together with chest clinic work. Ample scope for clinical research.

Applications, stating age, qualifications, nationality, experience, and the names of 2 referees, to be forwarded to the Group Secretary, Withington Hospital, Manchester, 20, within 7 days of appearance of this advertisement.

MANCHESTER REGIONAL HOSPITAL BOARD. South MANCHESTER HOSPITAL MANAGEMENT COMMITTEE. The Board invite applications from registered medical practitioners for the post of REGISTRAR in Plastic Surgery. The duties are largely at the main Plastic Unit at Wythenshawe Hospital, which is a general hospital with 71 plastic surgery beds. In addition the holder of this post attends other hospitals where plastic surgery is carried out under the direction of the Consultants.

Applications, stating age, qualifications, present post, and experience, together with the names of 2 referees, to the Group Secretary, Withington Hospital, Manchester, 20, immediately.

MANCHESTER REGIONAL HOSPITAL BOARD. Roch- DALE INFIRMARY. (109 Beds.) Locum ORTHOPÆDIC REGISTRAR required 1st October for approximately 6 weeks.

Written applications to be sent to Group Secretary, Central Offices, Birch Hill Hospital, Rochdale, as soon as possible.

MANCHESTER REGIONAL HOSPITAL BOARD. Bolton DISTRICT GENERAL HOSPITAL. (607 Beds.) RESIDENT REGISTRAR in General Surgery (Resident Surgical Officer). Recognised for F.R.C.S. The post is the senior resident surgical appointment and offers excellent practical experience.

Applications, stating age, nationality, qualifications, experience and the names of 2 referees, should be sent immediately to Group Secretary, Bolton and District Hospital Management Committee, The Royal Infirmary, Bolton.

MANCHESTER REGIONAL HOSPITAL BOARD invites applications for the post of MEDICAL REGISTRAR at the Devonshire Royal Hospital, Buxton, vacant on 1st December, 1957. The main duties will be in the Department of Physical Medicine with some duties in the Hospital. The post offers excellent opportunities in research. Previous physical medicine experience desirable. Interest in experimental work an advantage. Unfurnished accommodation on rental may be made available to male married applicant.

Applications, together with the names of 2 referees, to be forwarded to the Group Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport.

MANCHESTER REGIONAL HOSPITAL BOARD. SENIOR REGISTRAR in Chest Diseases, mainly at Manchester Chest Clinic. The person appointed will also have duties at Monsall Hospital (142 tuberculous and non-tuberculous beds), Manchester Northern Hospital (non-tuberculous outpatients) and in the thoracic surgery units at Park and Baguley Hospitals, and will later transfer to the Bolton area (Bolton Royal Infirmary, Bolton Chest Clinic, &c.).

Application forms from the Senior Administrative Medical Officer of the Board, Cheetwood-road, Manchester, 8, to be returned by 14th October, 1957.

MANCHESTER REGIONAL HOSPITAL BOARD. Sal- FORD HOSPITAL MANAGEMENT COMMITTEE. HOPE HOSPITAL. RESIDENT SURGICAL REGISTRAR required.

Applications to Group Secretary, Salford Royal Hospital, Salford, 3, before 5th October, 1957.

MANCHESTER, 23. WYTHENSHAWE HOSPITAL. SOUTH MANCHESTER HOSPITAL MANAGEMENT COMMITTEE. Applications are invited for the post of Locum SENIOR HOUSE OFFICER in Plastic Surgery at the above Hospital, for 10 weeks commencing 14th October, 1957. This Officer is the only House Officer for a Plastic Surgery Unit of 71 Beds which takes most of his time, but in addition there are some general surgical duties.

Applications, with the names of 2 referees, to the Group Secretary, Withington Hospital, Manchester, 20.

MANCHESTER (near). ROYAL MANCHESTER CHILD- REN'S HOSPITAL, PENDLEBURY, near MANCHESTER. SALFORD HOSPITAL MANAGEMENT COMMITTEE. Applications invited for resident appointment of SURGICAL HOUSE OFFICER, now vacant. Appointment tenable for 6 months and it is open to pre-registration graduates.

Applications, with testimonials or names of referees, to the Hospital Secretary not later than 7th October, 1957.

MORECAMBE. QUEEN VICTORIA HOSPITAL. RESIDENT SENIOR HOUSE OFFICER (surgical). The post is normally tenable 1 year and the successful applicant will be attached to the specialist Surgical Unit. Pos vacant now.

Applications, with names of 2 referees, to be addressed to the Group Secretary, Royal Lancaster Infirmary, Lancaster.

MAIDENHEAD HOSPITAL, Berkshire. Applications invited for post of HOUSE PHYSICIAN vacant 4th November. Pre-registration post.

Applications, stating age, nationality and qualifications, with names of 3 referees, to Secretary.

NEWCASTLE HOSPITAL MANAGEMENT COMMIT- TEE. SENIOR HOUSE OFFICER OPHTHALMOLOGIST (whole-time), Newcastle Hospital Management Committee, Eye Unit. Recognised for D.O. Hospitals—Newcastle General (838 Beds), Walker Gate (309—42 ophthalmic beds), Walker Accident (21 ophthalmic beds).

Applications, with names and addresses of 3 referees, to the Group Secretary, Newcastle General Hospital, Westgate-road, Newcastle upon Tyne, 4.

NEWCASTLE REGIONAL HOSPITAL BOARD. REGISTRAR ORTHOPÆDIC SURGEON (whole-time), resident or non-resident, for Darlington Group of hospitals. Single accommodation available.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. SENIOR REGISTRAR PATHOLOGIST (whole-time), non-resident, East Cumberland Group of hospitals—main hospital, Cumberland Infirmary, Carlisle (332 Beds).

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. REGISTRAR ANÆSTHETIST (whole-time), Tees-side Group of hospitals—main hospital, North Ormesby (184 Beds). Non-resident: near main hospital; resident male single accommodation available. Post recognised for F.F.A.R.C.S. examination.

Applications, with names and addresses of 3 referees, to Senior Administrative Medical Officer, Regional Hospital Board, Benfield-road, Newcastle upon Tyne, 6, within 14 days.

NEWCASTLE REGIONAL HOSPITAL BOARD. CUMBERLAND GROUP OF HOSPITALS. SENIOR REGISTRAR or REGISTRAR in Anæsthetics on Locum basis for a period of 2/3 months, required immediately.

Applications, naming 3 referees, to Senior Administrative Medical Officer, 72, Warwick-road, Carlisle.

NORTHAMPTON (near). CREATON HOSPITAL. (138 Beds.) Applications are invited from suitably qualified medical practitioners for the post of SENIOR HOUSE OFFICER. The Hospital is for the treatment of both pulmonary and non-pulmonary tuberculosis. There is a modern major Thoracic Surgical Unit for tuberculous and non-tuberculous diseases of the chest.

Applications, stating age, experience, and qualifications, together with the names and addresses of 2 referees, should be sent to the Secretary, Northampton and District Hospital Management Committee, General Hospital, Northampton.

NORTHWOOD, MIDDLESEX. MOUNT VERNON HOSPITAL. (551 Beds.) NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR required in the X-ray Diagnostic Department at above Hospital for 1 year in first instance.

Application forms obtainable from, and returnable to, the Group Secretary, Harefield and Northwood Group Hospital Management Committee, Mount Vernon Hospital, Northwood, Middlesex, by 5th October, 1957. Hospital may be visited by direct appointment.

NORWICH. ST. ANDREW'S HOSPITAL, Thorpe, NORWICH. Applications are invited from registered medical practitioners (Male or Female) for the appointment of SENIOR HOUSE OFFICER (psychiatric). The Hospital has 1250 Beds, an admission-rate of over 750 annually and affords comprehensive experience in psychiatry. The salary and conditions of service will be as laid down by the Ministry for Senior House Officers. Residential accommodation with board available.

Applications, stating age, qualifications, and full particulars of experience, together with the names and addresses of 2 referees, to be sent as soon as possible to the Medical Superintendent.

NOTTINGHAM. CITY HOSPITAL. (811 Beds.) Applications are invited for the post of RESIDENT PATHOLOGIST (Senior House Officer). Previous experience an advantage. Post vacant 14th November, 1957.

Applications, stating age, nationality, qualifications and experience, together with copies of not more than 3 testimonials, to be sent to the Group Secretary, Sherwood Hospital, Hucknall-road, Nottingham.

NOTTINGHAM. CITY HOSPITAL. (811 Beds.) Applications are invited for the post of HOUSE SURGEON, vacant 4th November, 1957. Recognised for pre-registration purposes.

Applications, stating age, nationality, qualifications and experience, together with copies of not more than 3 testimonials, to be sent to the Hospital Secretary, City Hospital, Hucknall-road, Nottingham.

NOTTINGHAM GENERAL HOSPITAL. A Senior HOUSE OFFICER (orthopædic and fracture) required as soon as possible. Post offers exceptional experience in traumatic surgery. LOCUM required in the meantime for any period.

Applications, stating age, qualifications and experience, together with copies of testimonials, to be sent to Group Secretary.

NOTTINGHAM GENERAL HOSPITAL. E.N.T. Depart- MENT. A SENIOR HOUSE OFFICER (E.N.T.) required at above Hospital. This post is recognised for the D.L.O. and F.R.C.S. examinations. Salary and conditions of service in accordance with Ministry regulations. Duties to commence about end September.

Applications, stating age, qualifications, experience and nationality, together with copies of testimonials, to be sent to Group Secretary.

OXFORD REGIONAL HOSPITAL BOARD. Senior REGISTRAR in Obstetrics and Gynæcology (resident) to the Combined Reading Hospitals (100 Beds). Applicants should preferably hold the M.R.C.O.G.

Applications on forms obtainable from the Secretary, Registrars Committee, 43, Banbury-road, Oxford, should reach him by 14th October.

OXFORD REGIONAL HOSPITAL BOARD. Registrar in Anæsthetics to the hospitals of the Reading area. The appointment, which is recognised for the F.F.A.R.C.S. Diploma, will be for 1 year and eligible for extension to 2 years. Single accommodation is available.

Applications, on forms obtainable from the Secretary, Registrar Committee, 43, Banbury-road, Oxford, should reach him by 22nd October.

OXFORD. UNITED OXFORD HOSPITALS. Applications invited for post of NON-RESIDENT REGISTRAR in the Tuberculous Meningitis Unit at the Osler Hospital, Headington, Oxford, commencing on 1st November, 1957. The post will be for 1 year in the first instance but eligible for extension to a second year.

Applications, on forms obtainable from the Administrator, Radcliffe Infirmary, Oxford, should be received not later than 5th October, 1957.

PORTSMOUTH GROUP HOSPITAL MANAGEMENT COMMITTEE. INFECTIOUS DISEASES HOSPITAL. SENIOR HOUSE OFFICER required with duties also on the Tuberculosis Wards and the Poliomyelitis Diagnostic and Respiratory Centre. Vacant 1st October, 1957.

Applications, stating age, experience and qualifications, together with the names of 2 referees, should be forwarded as soon as possible to E. H. HURRT.

St. Mary's Hospital, Milton-road, Portsmouth.

READING. BATTLE HOSPITAL. (391 Beds.) Applications are invited from registered medical practitioners for the post of RESIDENT JUNIOR HOUSE SURGEON in the Accident and Orthopædic Department. Post vacant 1st November, 1957. F.R.C.S. recognised. Also casualty duties.

Apply, stating age, qualifications with dates, nationality, present post, with 1 copy of recent testimonial, to Hospital Secretary.

READING COMBINED HOSPITALS. Area Department OF OBSTETRICS AND GYNÆCOLOGY. (100 Beds.) Applications are invited from registered medical practitioners, Male and Female, for the resident appointment of GYNÆCOLOGICAL HOUSE SURGEON at the Royal Berkshire Hospital, Reading. Vacant 8th October, 1957, and tenable for 6 months. Post recognised for M.R.C.O.G.

Write, stating age and qualifications with dates, nationality and present post, with copy of 1 recent testimonial, to Secretary.

ROCHDALE AND DISTRICT HOSPITAL MANAGE-MENT COMMITTEE. BIRCH HILL HOSPITAL. HOUSE OFFICER (obstetrics and gynæcology) required early November. Pre- or post-registration post of 6 months duration. Recognised for D.Obst.R.C.O.G.

Apply to Group Secretary, Central Offices, Birch Hill Hospital, Rochdale, at once.

ROMFORD, ESSEX. VICTORIA HOSPITAL. (99 Beds.) RESIDENT HOUSE PHYSICIAN (Male) required from 1st October, 1957. Not pre-registration appointment.

Applications should be forwarded to the Secretary, Romford Group Hospital Management Committee, Oldchurch Hospital, Romford.

ROMFORD GROUP HOSPITAL MANAGEMENT COM-MITTEE. CLINICAL ASSISTANT required on the staff of the Regional Ophthalmic Centre at Oldchurch Hospital, Romford, to undertake 1 outpatient session per week (Thursday morning) in the Eye Clinic at Tilbury and Riverside Hospital, Tilbury.

Applications to be sent to Group Secretary, Oldchurch Hospital, Romford, as soon as possible.

ROMFORD, ESSEX. OLDCHURCH HOSPITAL. (722 Beds.) SENIOR HOUSE OFFICER (ophthalmology).

Applications should be addressed immediately to the Group Secretary, Romford Group Hospital Management Committee, Oldchurch Hospital, Romford.

ROMFORD, ESSEX. OLDCHURCH HOSPITAL. (722 Beds.) RESIDENT SENIOR HOUSE OFFICER in Anæsthetics. Post recognised for F.F.A.R.C.S. Excellent opportunities exist at this Hospital for gaining tuition and experience in the administration of anæsthetics. The equipment is the most modern available.

Applications should be sent to Group Secretary, Romford Hospital Management Committee, at the Hospital as soon as possible.

SALFORD ROYAL HOSPITAL. Salford Hospital Manage-MENT COMMITTEE. Applications invited for the post of SENIOR HOUSE OFFICER in General Surgery (Assistant Resident Surgical Officer). The post is recognised for the F.R.C.S. and tenable for 1 year.

Applications to the Secretary, Salford Royal Hospital, Chapel-street, Salford, 3.

SLOUGH, BUCKINGHAMSHIRE. UPTON HOSPITAL. SENIOR HOUSE OFFICER (casualty) required, working with Casualty Registrar in busy Casualty Department. Experience given in plastic and orthopædic cases.

Applications, with names of 2 referees, to Secretary.

SHEFFIELD REGIONAL HOSPITAL BOARD. Whole-time NON-RESIDENT SENIOR REGISTRAR (psychiatry) required for duties at the Towers Hospital, Leicester, and at the Children's Psychiatric Clinics in Leicester and Leicestershire. Possession of D.P.M. essential. Appointment for 1 year in first instance reviewable annually.

Application forms and further details from Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield. Forms to be returned by 14th October, 1957.

SHEFFIELD. THE UNITED SHEFFIELD HOSPITALS. ROYAL INFIRMARY/ROYAL HOSPITAL UNITS. Applications invited for the non-resident post of REGISTRAR to the Department of Radiology at the above hospitals. Post vacant 1st December.

Applications, stating age, qualifications, and experience, with the names of 3 referees, should be sent not later than 12th October, 1957, to the Chief Administrative Officer, The United Sheffield Hospitals, West-street, Sheffield, 1.

SHEFFIELD. THE UNITED SHEFFIELD HOSPITALS BOARD OF GOVERNORS AND SHEFFIELD REGIONAL HOSPITAL BOARD. Reciprocal Training Scheme for Senior Registrars Whole-time NON-RESIDENT SENIOR MEDICAL REGISTRAR required with initial tenure of appointment at the City General Hospital, Sheffield. The Hospital has teaching affiliations with Sheffield University and most of the Consultant staff have the status of Clinical Teachers. There is a Professorial Medical Unit and a Regional Cardiological Department. Appointment for 1 year in first instance and renewable thereafter annually. The successful candidate will be transferred to the Teaching Hospitals for the second phase of the appointment in accordance with arrangements under the Reciprocal Training Scheme. Renewal of appointment and transfer to the Teaching Hospitals will be subject to satisfactory work and progress.

Further details and form of application from the Senior Administrative Medical Officer, Sheffield Regional Hospital Board, Old Fulwood-road, Sheffield, 10. Forms to be returned by 7th October, 1957.

SHREWSBURY. EYE, EAR AND THROAT HOSPITAL. SENIOR HOUSE OFFICER (E.N.T.) Duties at E.N.T. Hospital (68 Beds) and Copthorne Hospital (168 Beds). Post recognised for the D.L.O.R.C.S. Vacant 1st November, 1957.

Applications, with copy testimonials, to the Group Secretary, Shrewsbury Hospital Group, Royal Salop Infirmary, Shrewsbury.

SHREWSBURY. ROYAL SALOP INFIRMARY/COP-THORNE HOSPITAL. (500 Beds.) HOUSE PHYSICIAN, pre-registration candidates eligible. Vacant 24th October, 1957.

Applications, with copy testimonials, to Group Secretary, Shrewsbury Hospital Group, Royal Salop Infirmary, Shrewsbury.

SHREWSBURY. ROYAL SALOP INFIRMARY/COP-THORNE HOSPITAL. (500 Beds.) SHREWSBURY HOSPITAL GROUP. HOUSE SURGEON, vacant 1st November, 1957. Pre-registration candidates eligible. Recognised for the F.R.C.S.

Applications, with copy testimonials, to Group Secretary, Royal Salop Infirmary, Shrewsbury.

SHREWSBURY. ROYAL SALOP INFIRMARY AND COPTHORNE HOSPITAL. (500 Beds.) SENIOR HOUSE OFFICER (gynæcological). 50 gynæcological beds and 2 House Surgeons. Posts recognised for M.R.C.O.G. Vacant 4th November, 1957.

Applications, with copy testimonials, to Group Secretary, Shrewsbury Hospital Group, Royal Salop Infirmary, Shrewsbury.

SCOTLAND. WESTERN REGIONAL HOSPITAL BOARD. Applications are invited for the following appointments, which will be for 1 year in the first instance :—

SENIOR REGISTRAR in Ophthalmology based at the Glasgow Ophthalmic Institution.

SENIOR REGISTRAR in Radiodiagnosis based at the Western Infirmary, Glasgow.

REGISTRAR in Radiodiagnosis based at the Western Infirmary, Glasgow.

REGISTRAR in Obstetrics and Gynæcology at the Royal Maternity Hospital and Royal Infirmary, Glasgow.

REGISTRAR in Pathology based at the Victoria Infirmary, Glasgow.

REGISTRAR in Surgery based at the Vale of Leven Hospital, Alexandria, Dunbartonshire.

Applications (12 copies), stating date of birth, qualifications, experience, present appointment, and the names of 3 referees, to reach the Secretary, Western Regional Hospital Board, 64, West Regent-street, Glasgow, C.2, by 12th October, 1957.

SKIPTON (near). GRASSINGTON HOSPITAL. (208 Beds.) SENIOR HOUSE OFFICER required for the above Hospital, which provides treatment for tuberculous patients, men and women. Accommodation available for single applicants.

Applications to Medical Superintendent.

SOUTHAMPTON. ROYAL SOUTH HANTS HOS-PITAL. (274 Beds.) RESIDENT HOUSE SURGEON required. Pre-registration candidates eligible.

Applications, with copies of recent testimonials, should be forwarded to Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SOUTHAMPTON. ROYAL SOUTH HANTS HOSPITAL. 274 Beds. Recognised for F.R.C.S.) ORTHOPÆDIC HOUSE SURGEON (post recognised for Pre-registration Service and tenable for 6 months) and SENIOR HOUSE OFFICER (orthopædic). The Hospital is the centre to which all trauma from a large industrial town and port is directed thus providing excellent experience in the treatment of traumatic conditions; patients with orthopædic conditions are also drawn from a wide area.

Applications, with copies of testimonials, should be sent as soon as possible to the Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton.

SOUTHAMPTON. ROYAL SOUTH HANTS HOS-PITAL. (274 Beds.) RESIDENT HOUSE PHYSICIAN required. Pre-registration candidates eligible.

Applications, with copies of testimonials, should be forwarded to Group Secretary, Southampton Group Hospital Management Committee, Bullar-street, Southampton, as soon as possible.

SOUTHALL, MIDDLESEX. ST. BERNARD'S HOS-PITAL FOR NERVOUS AND MENTAL DISORDERS. Applications are invited for the post of SENIOR HOUSE OFFICER. Facilities are afforded junior staff to become versed in all branches of psychiatry. National Health Service salary and conditions.

Applications, giving full details and copies of 3 recent testimonials, should be sent to the Physician-Superintendent within 14 days of the appearance of this advertisement.

SOUTH CHESHIRE HOSPITAL MANAGEMENT COMMITTEE. SENIOR HOUSE OFFICER (anæsthetics), vacant mid-October. 6–12 months. Duties mainly at Surgical Hospital, Crewe (120 Beds), and Maternity Unit, Barony Hospital, Nantwich. Recognised D.A. Previous experience not necessary. New theatres with perfect air conditioning and later anæsthetic apparatus and equipment. Personal supervision and teaching by Consultant.

Apply immediately, stating age, qualifications, &c., with names of 2 referees, to the Group Secretary, Barony Hospital, Nantwich, Cheshire.

SOUTH EAST METROPOLITAN REGIONAL HOSPITAL BOARD. Applications are invited for an appointment as Whole-time SENIOR REGISTRAR in Psychiatry to fill a vacancy in the approved trainee establishment at St. Augustine's Hospital, Chartham Down, near Canterbury. Candidates should possess the D.P.M. and have had wide experience in general medicine. The appointment will be in accordance with the terms and conditions of service of hospital medical and dental staffs (England and Wales) and will be for 1 year in the first instance. The post will include opportunities for gaining further experience in a wide range of psychiatry including attendance at adult outpatient clinics. A house will be available for a married practitioner.

Applications, giving particulars of age, qualifications and experience with relevant dates, together with the names and addresses of 3 referees, should be sent to the Secretary, Registrars Committee, South East Metropolitan Regional Hospital Board, 11, Portland-place, London, W.1, not later than 12th October, 1957.

SULLY HOSPITAL, Sully, Glamorgan. Regional Thoracic CENTRE. (324 Beds.) SENIOR HOUSE OFFICER (surgical) required. Experience will be gained in investigation and treatment of chest and heart conditions.

Form of application from Group Secretary, Cardiff Hospital Management Committee, 44, Cathedral-road, Cardiff.

ST. ALBANS, HERTFORDSHIRE. CELL BARNES HOSPITAL. NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR required at above Hospital. This is a modern hospital where 750 mental defectives of all types and ages are under care. Approved for D.P.M. Hospital may be visited by direct appointment.

Application forms obtainable from the Group Secretary. Harperbury Hospital, St. Albans, Herts, and returnable by 5th October, 1957.

ST. ALBANS CITY HOSPITAL, St. Albans, Hertfordshire. (384 Beds.) HOUSE SURGEON (House Officer grade) required for 1 of the 2 surgical teams. Post recognised for F.R.C.S. Post vacant 26th October, 1957, and tenable for 6 months. Preference given to candidates seeking post under the Medical Act, 1950.

Applications to Secretary, Mid Herts Group Hospital Management Committee, Bleak House, Catherine-street, St. Albans.

ST. ALBANS CITY HOSPITAL, St. Albans, Hertfordshire. (384 Beds.) HOUSE PHYSICIAN (House Officer grade) required for 1 of the 2 medical firms for duties mainly on the acute wards. Post vacant approximately 21st October, 1957, and tenable for 6 months. Preference given to candidates seeking post under the Medical Act, 1950.

Applications to Secretary, Mid Herts Group Hospital Management Committee, Bleak House, Catherine-street, St. Albans.

ST. ALBANS CITY HOSPITAL, St. Albans, Hertfordshire. (384 Beds.) HOUSE PHYSICIAN (House Officer grade) required for duties mainly in the Pædiatric Department. Post vacant approximately 21st October, 1957, and tenable for 6 months. Preference given to candidates seeking pre-registration post under the Medical Act, 1950.

Applications to Secretary, Mid Herts Group Hospital Management Committee, Bleak House, Catherine-street, St. Albans.

STOCKPORT. STEPPING HILL HOSPITAL. (529 Beds.) **STOCKPORT AND BUXTON HOSPITAL MANAGEMENT COMMITTEE.** Applications are invited for the post of SENIOR HOUSE OFFICER (pædiatrics). The post, which may be either resident or non-resident, becomes vacant on 1st December, 1957.

Applications, stating age, qualifications and experience, together with copies of 2 testimonials, to be addressed to the Secretary, Stockport and Buxton Hospital Management Committee, 59B, Shaw-heath, Stockport.

STOKE-ON-TRENT. NORTH STAFFORDSHIRE ROYAL INFIRMARY. GYNÆCOLOGY DEPARTMENT. SENIOR HOUSE OFFICER required. Post vacant shortly. Recognised for M.R.C.O.G. (surgery). Experience in abnormal obstetrics available, but the work is mainly gynæcological.

Detailed applications, with copy testimonials, to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. HOUSE OFFICER (pædiatrics) required, vacant now. Pre-registration post. Recognised for D.C.H.

Detailed applications, with copy testimonials, to Group Secretary, Princes-road, Stoke-on-Trent.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. SENIOR HOUSE OFFICER (obstetrics and gynæcology) required, post vacant mid-November. Recognised M.R.C.O.G. and D.Obst.R.C.O.G.

Detailed applications, with copy testimonials, to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent, as soon as possible.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. (815 Beds.) HOUSE OFFICER (general surgery) required, vacant now. Pre-registration post. Hospital recognised for F.R.C.S.

Detailed applications, with copy testimonials, to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent.

STOKE-ON-TRENT. CITY GENERAL HOSPITAL. Applications invited for HOUSE OFFICER (medical)—2 posts—both vacant mid-October. Recognised pre-registration.

Detailed applications to Group Secretary, Hospital Management Committee, Princes-road, Stoke-on-Trent.

SWINDON AND DISTRICT HOSPITAL MANAGEMENT COMMITTEE. ST. MARGARET'S HOSPITAL, STRATTON. Applications invited for the post of RESIDENT SENIOR HOUSE OFFICER for Pædiatric Unit. Post recognised for D.C.H., permits time for postgraduate study; vacant 6th October.

Full details, with names of 3 referees, to Secretary, 7, Okus-road, Swindon, Wilts, as soon as possible.

TAPLOW, near MAIDENHEAD. CANADIAN RED CROSS MEMORIAL HOSPITAL. RESIDENT MEDICAL REGISTRAR required.

Application forms from, and returnable to, Secretary, Windsor Group Hospital Management Committee, Alma-road, Windsor, by 5th October.

TAUNTON AND SOMERSET HOSPITAL. Applications are invited for the post of SENIOR HOUSE OFFICER (casualty and orthopædic). Post vacant mid-October.

Applications, stating age, nationality, and qualifications, together with the names of 2 referees, should be forwarded to the Group Secretary, Taunton Hospital Management Committee, Taunton and Somerset Hospital, Musgrove Park Branch, Taunton, Somerset.

TAUNTON AND SOMERSET HOSPITAL. Senior HOUSE OFFICER (general medicine), required end of October. Post also gives opportunity of work in Area Pathological Laboratory if desired.

Applications, stating age, nationality, and qualifications, together with the names of 2 referees, should be forwarded to the Group Secretary, Taunton Hospital Management Committee, Taunton and Somerset Hospital, Musgrove Park Branch, Taunton, Somerset.

TORQUAY, TORBAY HOSPITAL. Resident Senior HOUSE OFFICER (surgery) required immediately. Post recognised for F.R.C.S. There is a complement of 6 Resident House Officers.

Applications, stating qualifications, age, nationality, with copy testimonials (quoting Ref. F.955/83), to the Group Secretary, Torquay District Hospital Management Committee, Torbay Hospital, Torquay, S. Devon.

TREDEGAR GENERAL HOSPITAL, Monmouthshire. RHYMNEY AND SIRHOWY VALLEYS HOSPITAL MANAGEMENT COMMITTEE. RESIDENT SURGICAL OFFICER (Junior Hospital Medical Officer grade) required for Surgical Unit at above Hospital. Duties are those of Assistant to General Surgeon; staff includes also House Surgeon. Commodious family flat.

Apply, with full particulars and stating names of 2 referees, to Secretary.

TUNBRIDGE WELLS (near). PEMBURY HOSPITAL, PEMBURY. Applications invited for the post of RESIDENT ANÆSTHETIST (Senior House Officer). Post vacant 1st November, 1957. The post is tenable for 12 months in the first instance and recognised for the D.A. and the F.F.A.R.C.S.

Apply, stating age, qualifications, and experience, together with 3 testimonials, to Group Secretary, Sherwood Park, Pembury-road, Tunbridge Wells.

WELSH REGIONAL HOSPITAL BOARD.

REGISTRAR (general surgery), Pembroke County War Memorial Hospital, Haverfordwest (resident or non-resident).

REGISTRAR (general surgery), based at Bridgend General Hospital, Bridgend (381 Beds), to serve Mid-Glamorgan Hospital Management Committee. May also be expected to serve other hospitals in Group. Hospital recognised for F.R.C.S. Resident/non-resident.

Subject to review end of first year.

Application forms from Senior Administrative Medical Officer, Temple of Peace, Cathays Park, Cardiff, within 14 days.

WOKING AND CHERTSEY GROUP LABORATORY. Applications are invited for the post of RESIDENT CLINICAL PATHOLOGIST (Senior House Officer). The post is 1 of 2, and involves a half-share in the emergency service. Training will be available in all branches of clinical pathology. Post tenable for 1 year. Salary £819 10s. p.a. (deduction for board and lodging £150 p.a.).

Applications, stating age, qualifications, &c., together with the names of 2 referees, should be sent as soon as possible to the Director, Group Laboratory, St. Peter's Hospital, Chertsey, Surrey.

WORCESTER. RONKSWOOD HOSPITAL. (312 Beds.) Locum RESIDENT ANÆSTHETIST (Senior House Officer grade) required immediately for approximately 2 months.

Applications to Hospital Secretary.

WORCESTER (near). POWICK HOSPITAL. Applications are invited for the post of JUNIOR HOSPITAL MEDICAL OFFICER (resident or non-resident). The post offers experience in all branches of psychiatry, including all forms of modern treatment and outpatient clinics. The Hospital has a high admission-rate, is recognised for the D.P.M., and has associated Child Guidance Clinics and a Mental Deficiency Institute similarly recognised. Arrangements are made for Medical Officers to attend at the Birmingham Medical School for instruction in neurology.

Applications, with full details and the names of 2 referees, to be forwarded to the Medical Superintendent.

WIGAN (near). BILLINGE HOSPITAL. Registrar in Psychiatry. The post offers good experience under Consultant Psychiatrist. Main centre at Billinge Hospital where there is an active psychiatric unit with modern treatment and over 300 admissions annually. Post recognised for D.P.M.

Applications, with names of 2 referees, to Secretary, Wigan and Leigh Hospital Management Committee, Knowsley House, Wigan.

WIGAN. ROYAL ALBERT EDWARD INFIRMARY. SENIOR HOUSE OFFICER for duty in the Pædiatric Department at Wigan Infirmary, and also to undertake neonatal work at Billinge Hospital. Post recognised for D.C.H. Consultant Pædiatrician-in-charge. Post vacant early October.

Applications, with names of 2 referees, to the Secretary, Royal Albert Edward Infirmary, Wigan.

WINCHESTER AND LORD MAYOR TRELOAR GROUPS. SOUTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. REGISTRAR in Anæsthetics (Registrar grade) required. Alton General Hospital with duties at Lord Mayor Treloar and Henry Gauvain Hospitals, Alton, and the Royal Hampshire County Hospital, Winchester. Post recognised for F.F.A.R.C.S. and is resident or non-resident. Vacant 1st January, 1958.

Forms of application, obtainable from Group Secretary, Royal Hampshire County Hospital, Winchester, must be completed and returned by 12th October, 1957.

WINCHESTER. ROYAL HAMPSHIRE COUNTY HOSPITAL. HOUSE PHYSICIAN (obstetrics) required. Post recognised D.Obst.R.C.O.G. Vacant 30th November.

Applications, with copies of 2 testimonials, to the Group Secretary.

WINCHESTER. ROYAL HAMPSHIRE COUNTY HOSPITAL. (315 Beds.) SENIOR HOUSE OFFICER (orthopædics) required. Post recognised F.R.C.S. Wide experience available under Area Orthopædic team. Appointment for 6 months in first instance. Vacant 11th November.

Applications, with copies of 2 testimonials, to the Group Secretary.

WATFORD AND DISTRICT PEACE MEMORIAL HOSPITAL. (208 Beds.) Applications are invited for the post of CASUALTY OFFICER (Senior House Officer), vacant October. Post recognised for F.R.C.S. Salary according to National Health scale.

Apply, with copies of 2 testimonials, to the Administrator, Peace Memorial Hospital, Watford, Herts.

WATFORD CHEST CLINIC, Peace Memorial Hospital, WATFORD. NORTH WEST METROPOLITAN REGIONAL HOSPITAL BOARD. Applications invited for the post of REGISTRAR at the above Clinic and associated beds (tuberculosis 47, chest medicine 16) at Shrodells and Holywell Hospitals. This is a new Chest Clinic. Experience in general medicine and tuberculosis work, including refill techniques, is essential. This chest unit is closely associated with Harefield Hospital, the Physician-in-charge being on the Consultant staff of this Hospital. Applicants invited to visit the clinic and should contact the Physician-in-charge.

Application form obtainable from, and returnable to, the Secretary, West Herts Group Hospital Management Committee, 9, Rickmansworth-road, Watford, Herts, by not later than 10 days after the appearance of this advertisement.

WATFORD CHEST CLINIC, Peace Memorial Hospital, WATFORD. Locum REGISTRAR required immediately for work at the above Chest Clinic and beds (tuberculosis and chest medicine) at associated hospitals. Experience of refills essential. Car is desirable and allowances are paid.

Apply immediately to the Physician-in-charge (Telephone: Watford 9266).

WOLVERHAMPTON. NEW CROSS HOSPITAL. (634 Beds.) Pre-registration HOUSE OFFICER in Medicine. Vacant 1st October.

Applications to the Hospital Secretary.

WOLVERHAMPTON. NEW CROSS HOSPITAL. (634 Beds.) Pre-registration HOUSE OFFICER in General Surgery. Vacant late September.

Applications to the Hospital Secretary.

YORK. FAIRFIELD SANATORIUM (68 Beds), CITY HOSPITAL (256 Beds) AND COUNTY HOSPITAL (266 Beds). Required in December, 1957, SENIOR HOUSE OFFICER in Chest Diseases and General Medicine (non-resident) to spend half time at Fairfield Sanatorium and at the City Hospital where 8 beds are reserved for investigation of chest cases, and at the Chest Clinic where outpatient refill clinics are held, and remainder of time at the County and City Hospitals in the Department of General Medicine. Previous experience in treatment of tuberculosis an advantage.

Applications, giving age, nationality, experience, qualifications and names of 2 referees, to Group Secretary, York A and Tadcaster Hospital Management Committee, Bootham Park, York.

DUBLIN. ST. KEVIN'S HOSPITAL. The Dublin Board of Assistance invites applications for appointment to 2 posts of REGISTRAR in Obstetrics. Period of appointment: 1 year which may be extended for further periods to a total of 3 years. Salary: first year £650; second year £750; third year £850 with full board and residence plus temporary bonus at the rate of 10% on first £300 and 6½% on balance of remuneration. A further £100 p.a. is payable on obtaining certain higher qualifications.

Full particulars and application form may be obtained from the Establishment Department, 1, James's-street, Dublin. Latest date for receipt of completed application forms 8th October, 1957.

U.S.A. CAMBRIDGE, MASSACHUSETTS. Applications are invited for the positions of RESIDENCIES in Anesthesia for a 2-year period beginning 1st July and 1st September, 1957. Salary $1800 first year and $3600 second year and full maintenance. Training in all branches of anesthesia. Affiliation with other hospitals.

Applications, stating age, nationality, qualifications, and experience, together with the names of their referees, should be forwarded to the Director of Anesthesiology, P.O. Box 89, Cambridge, Massachusetts. Travelling expenses to and from the U.S.A. will be paid. Particulars will be sent as soon as application is received. Please enclose recent photograph with application.

WARWICK (near). CENTRAL MENTAL HOSPITAL. (1400 Beds.) SENIOR HOUSE OFFICER. Neurosis Unit, adult and child psychiatry clinics, departments of electroencephalography, occupational therapy, psychology and social work. Recognised for D.P.M. Flat available.

Applications, with names and addresses of 3 referees, to Medical Superintendent within 14 days.

Public Appointments

GOVERNMENT OF HONG KONG. Male Radiologists (diagnostic) required. Candidates must possess qualifications registrable in United Kingdom and D.M.R.D. Appointment on contract for 3 years. Emoluments include basic salary on scale ranging from £1095 to £2175 a year, expatriation pay from £210 to £311 5s. a year, variable cost-of-living allowance of £43 16s. a year for single man, £186 approximately a year for married man without children, and £328 10s. a year for married man with children. 2 increments in scale allowed for possession of D.M.R.D. and entry point also depends on experience. Thus a married man with children and 1 years experience after Housemanship would receive approximately £1828 a year. Free passages for Officer, wife, and up to 3 children under 18 years. Pending quarters becoming available, hotel or hostel accommodation provided. Maximum charge for quarters, hotel, or hostel accommodation one-seventh of basic salary. Income-tax at local rates. Climate favourable. Educational facilities available.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD. 117/51/011).

GOVERNMENT OF SARAWAK. Male Medical Officers required in Sarawak to undertake travelling duties in country districts. Must be prepared for arduous travelling between widely separated villages; warm welcome, however, from friendly villagers. Candidates must possess qualifications registrable in United Kingdom and must be unmarried. Appointment on contract for 3 years with gratuity (taxable) of 12½% of salary (including expatriation pay) for each completed period of 1 month, payable on completion of contract. Candidates from National Health Service may retain superannuation rights (up to 6 years) and receive gratuity (taxable) of 20% of aggregate salary at end of engagement. Salary scale £1218–£1988 a year, starting salary depending on qualifications and experience. In addition expatriation pay varying from £252 to £336 a year. Free furnished quarters and free passages provided. Income-tax at local rates. Local leave permitted and generous home leave on completion of service.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD. 117/24/015).

GOVERNMENT OF MAURITIUS. Applications invited from doctors with qualifications registrable in U.K. for following posts:—

SENIOR MEDICAL OFFICER for Public Health Administration in 1 or more districts, particularly control of building, hygienic condition of premises, factories, shops, restaurants, warehouses, &c. Control of epidemic diseases, rodent control, port health, night soil and scavenging and all matters connected with environmental hygiene and health education. Candidates must possess D.P.H. Salary scale £1066 10s.–£1561 10s. a year. Cost-of-living allowance 9% of basic salary.

ASSISTANT RADIOLOGIST for therapeutic and diagnostic work and other duties as required. Experience in radiodiagnosis and therapy an advantage. Salary scale £805 10s.–£1426 10s. a year. Cost-of-living allowance 9% of salary up to £900 a year and 9% on salary over £900 a year.

Appointments on contract for 3 years with gratuity (taxable) from £37 10s. to £50 a quarter on satisfactory completion of contract. Officers not allocated Government quarters may be reimbursed difference between approved rent paid for a furnished private house (subject to a maximum of £22 10s. a month) and the 10% of salary normally paid for a Government house. Officers in hotel or boarding house regarded as paying rent for first 21 days at one-half and thereafter one-quarter of board and lodging charge for himself and family. Income-tax at local rates. Free passages.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD. 117/52/021).

GOVERNMENT OF THE FEDERATION OF RHODESIA AND NYASALAND. MINISTRY OF HEALTH. Vacancies: RADIOLOGISTS. Applications are invited for appointment as Radiologists in the Ministry of Health, with fixed salary at the rate of £2350 p.a. Duties will include radiodiagnosis, radiotherapy, and the training of Radiographers for the M.S.R. Diploma.

Application forms and further particulars from the Secretary (R), Rhodesia House, 429, Strand, London, W.C.2. Closing date 26th October.

NORWICH. CITY AND COUNTY OF NORWICH. Applications are invited for the post of DEPUTY MEDICAL OFFICER OF HEALTH AND DEPUTY PRINCIPAL SCHOOL MEDICAL OFFICER from registered medical practitioners holding the Diploma in Public Health or an equivalent qualification. Salary scale £1486 13s. 4d. rising by annual increments of £55 (4) and 1 of £50 to £1756 13s. 4d. Car essential—usual allowance.

For particulars and application forms apply to the Medical Officer of Health, 68, St. Giles'-street, Norwich, by whom applications should be received not later than 5th October, 1957.

NOTTINGHAMSHIRE COUNTY COUNCIL. Public HEALTH DEPARTMENT. Applications are invited for the appointment of MEDICAL OFFICER for Mental Health from registered medical practitioners with special experience in mental health. The possession of a Diploma in Psychological Medicine will be an advantage. Salary £1520–£50–£1570–£55–£1955 p.a.

Application forms and conditions of appointment from the County Medical Officer, County Hall, Trent Bridge, Nottingham. Applications by 21st October, 1957.

A. R. DAVIS, Clerk of the County Council.

HER MAJESTY'S OVERSEAS CIVIL SERVICE. Somaliland Protectorate. MEDICAL OFFICER with qualifications registrable in United Kingdom required for general medical duties, including simple surgery and, if necessary, training of dressers. Salary scale from £1116 to £1836 a year, plus temporary (non-pensionable) cost-of-living allowance of 10% of salary subject to maximum of £162. Commencing salary determined by qualifications and experience. Pension earned at rate of 1/600th of final pensionable emoluments for each completed month of service. Furnished quarters at low rental. Free passages in both directions for Officer, wife, and up to 4 children under 18 years. No income-tax. Tour of service 15–21 months, after which generous home leave granted. Local leave also granted.

Application forms from Director of Recruitment, Colonial Office, London, S.W.1 (quoting No. BCD. 117/5/01).

NAVY, ARMY AND AIR FORCE INSTITUTES. Applications are invited from general practitioners in the undernoted towns for the appointment in a part-time capacity as MEDICAL OFFICERS to this Corporation. Successful applicants would be required to examine and report on the condition of employees of the Corporation who may be referred to them from time to time. Fees for this work will be paid on a scale agreed with the British Medical Association.

Applications, giving details of qualifications and experience, should be sent to the Chief Medical Officer, Navy, Army and Air Force Institutes, Kennington-lane, London, S.E.11, not later than 5th October, 1957.

The towns for which applications are invited are :—

KINGS LYNN	PETERBOROUGH	LINCOLN
LEICESTER	NOTTINGHAM	GRIMSBY

WEST HARTLEPOOL. COUNTY BOROUGH OF WEST HARTLEPOOL. Applications are invited for the appointment of ASSISTANT MEDICAL OFFICER OF HEALTH from registered medical practitioners possessing the D.P.H. or D.C.H. The duties will be mainly in connection with Maternity and Child Welfare Services but the person appointed will be required to carry out such other duties (e.g., School Health Service duties) as may from time to time be allocated by the Medical Officer of Health. The appointment will be subject to the Whitley Council scale and conditions. Salary £1050 p.a.–£50–£1200–£55–£1475 p.a., according to experience. A car allowance of £75 p.a. is normally payable. The appointment will be subject to a medical examination for superannuation purposes and to 2 months notice in writing on either side. Canvassing will be a disqualification, and candidates must disclose any relationship to members of the Council.

Applications, stating the names and addresses of 3 referees, must be received by the Medical Officer of Health, Durham House, Victoria-road, West Hartlepool, not later than 14th October, 1957. ERIC J. WAGGOTT, Town Clerk.

Municipal Buildings, West Hartlepool, 19th September, 1957.

WESTMINSTER CITY COUNCIL AND HOLBORN BOROUGH COUNCIL. Joint appointment of DEPUTY MEDICAL OFFICER OF HEALTH (permanent superannuable post). Salary £2050–£105–£2365 p.a. Applicants to be registered medical practitioners and to hold a registered Public Health qualification; age under 46 years at 30th September, 1957. The person appointed will act as Deputy Medical Officer of Health for the 2 boroughs. His services will be allocated in the proportion of three-fourths to Westminster and one-fourth to Holborn.

Applications (marked "Deputy Medical Officer of Health"), stating age, war service, qualifications, present and past appointments, with names of 3 referees, to the Town Clerk, Westminster City Hall, Charing Cross-road, London, W.C.2, by 11th October, 1957.

WEST MIDLANDS GAS BOARD. Applications are invited for the post of ASSISTANT MEDICAL OFFICER, the successful candidate for which may be required to undertake the clinical and other duties of an Industrial Medical Officer in all parts of the Board's area, but will work principally in the Industrial area adjacent to Birmingham. The commencing salary will be not less than £1400 p.a. The post is pensionable, and the successful candidate may be required to undergo a medical examination.

Applications, giving full details of age, qualifications, experience and the names of 2 referees, should be sent to the Industrial Relations Officer, West Midlands Gas Board, 6, Augustus-road, Birmingham, 15, not later than 19th October, 1957.

J. SWAN, Secretary to the Board.

General Practice

For an Executive Council post (England and Wales) apply on form E.C.16A obtainable from the council. Mark envelope "Vacancy"

CRANBROOK, KENT. Applications invited for Vacancy (rural) due to death. List at present approximately 2620. Existing surgery accommodation likely to be available, but not residence. Apply on E.C.16A before 12th October, 1957, to—

F. E. MILES, Clerk, Kent and Canterbury Executive Council.
11, Station-road, Maidstone.

MIRFIELD, YORKSHIRE. Applications are invited for VACANCY, chiefly urban. List at present approximately 1789. Residential and surgery accommodation available for purchase. Apply on Form E.C.16A, to the undersigned, from whom further particulars may be obtained, not later than 12th October, 1957.

C. H. STABLER, Clerk, West Riding Executive Council.
5, St. John's-north, Wakefield.

OXFORD. Applications are invited for Vacancy (City of Oxford) due to death. List as at 1st July, 1957—5093. Position regarding house and surgery accommodation not yet clarified. Apply by 19th October, 1957, on Form E.C.16A to—

V. R. PARRY,
Clerk of the Oxford County and City Executive Council.
73, George-street, Oxford.

MERTON AND MORDEN (Merton Park). Applications are invited for VACANCY due to resignation in above urban district (Intermediate). Practice of a female medical practitioner for about 35 years. List about 1100. Resigning doctor's residence and surgery not available. Applications on Form E.C.16A, to reach the undersigned not later than 11th October, 1957.

S. H. BENNETT, Clerk of the Council.
187, Ewell-road, Surbiton.

READING EXECUTIVE COUNCIL. Applications are invited from registered medical practitioners for VACANCY in populous area of the Borough. Classification—Intermediate. List at present approximately 2100, including County patients. Residence and surgery available subject to negotiation with owner. Apply on Form E.C.16A before 9th October, 1957, to—

N. W. AUSTIN, Clerk of the Council.
10, Gun-street, Reading, Berks.

Exchange N.H. Practice, South Staffs, 9 miles Birmingham, 1100 units (increasing). Modern bungalow, for similar Northern Counties, Yorks preferred.—Address, No. 331, THE LANCET Office, 7, Adam-street, Adelphi, London, W.C.2.

Hospital Services : Non-Medical Appointment

SHEFFIELD. THE UNITED SHEFFIELD HOSPITALS. BIOCHEMIST (Senior or Basic grade, according to experience), required for the above group of Teaching Hospitals. The successful candidate will work primarily at the Jessop Hospital for Women, and be responsible to the Consultant Pathologist for routine biochemical work and for endocrine assay work. A knowledge of steroid chemistry is desirable. The appointment is in accordance with Whitley conditions.

Applications within 7 days to the Chief Administrative Officer, West-street, Sheffield, 1.

Miscellaneous

British Overseas Airways Corporation require a Medical Officer in the Corporation's Medical Service. Applicants should be between 28 and 34 years of age, with good academic qualifications and should possess a sound standard of clinical medicine. R.A.F. experience in the medical care of aircrew will be an advantage. The successful applicant will be based at London Airport, and the work will primarily consist of clinical examinations of flying staff and general medical duties in connection with the Corporation's Medical Service and will involve flying at home and overseas. Commencing salary will be in the range of £1785–£2170 p.a. according to age, qualifications and experience. The successful candidate will be required to join the Corporation's pension scheme.

Applications should be made, together with details of professional qualifications and experience to the Chief Personnel Officer, B.O.A.C. Headquarters, London Airport, Hounslow, Middlesex. The closing date for receipt of applications will be 11th October, 1957.

British European Airways invite applications for 2 medical posts of Assistant Medical Officer in the Corporation's Medical Service, based in United Kingdom. Applicants (Male) must be between 30 and 40 years of age and hold a British medical registration. Preference will be given to candidates with experience of aviation medicine or general practice. Commencing salary according to experience will be within the current B.M.A. range for the post (£1400–£1700). Initially the posts will be temporary appointments for 12 months but successful candidates will be eligible for consideration for a permanent appointment after the satisfactory completion of this period, which will require membership of the Corporation's pension scheme.

Application forms can be obtained from the Establishments Officer, Personnel Dept., B.E.A., Keyline House, Ruislip, Middx., to whom they should be returned, together with a recent photograph, by 14th October, 1957.

Assam. A British Medical Officer is required for a group of Tea Estates; age 28–36 years; tropical clinical and hygiene experience an advantage. Basic salary £2070 p.a. for 3-year agreement which is renewable, plus marriage and family allowances; car allowance additional; provident fund. Bungalow, essential furniture and servants provided.—Applications, with copies of 3 testimonials and the names of 3 other persons for reference purposes, to: Address, No. 333, THE LANCET Office, 7, Adam-street, Adelphi, London, W.C.2.

Middlesex Local Medical Committee. Applications are invited from registered general medical practitioners, practising or recently practising in Middlesex, for the post of part-time Secretary to the Middlesex Local Medical Committee. The successful applicant should be familiar with Committee procedure and have an intimate knowledge of the National Health Service Acts, and the relevant Regulations made thereunder, and would be required to exercise general supervision over the Committee's staff and offices. The salary payable is 1000 guineas p.a., together with travelling expenses at the British Medical Association scale, for an initial term of 3 years. Further details may be obtained on application to the Chairman.

A written application containing full details of the applicant's medical and medico-political experience, together with details of the size of his present or recent practice, and the names of 2 referees, should be sent to the Chairman of the Middlesex Local Medical Committee, Tavistock House (North), Tavistock-square, W.C.1, by 18th October.

"Pregnancy Diagnosis by the Xenopus Method," 24-hour service. Send specimens of urine and £1 1s. fee. Hæmatology, Biochemistry, Flame Photometry.—WELBECK BIOLOGICAL LABORATORIES, 26, Park-crescent, Portland-place, W.1 (MUSeum 5386–7).

Applicants for posts requiring testimonials copied or duplicated should communicate with MANTON SECRETARIAL SERVICE LTD., 98, Victoria-street, S.W.1 (Phone: VICtoria 0141), who are specialists in this kind of work.

PUBLISHED by the PROPRIETORS, THE LANCET LIMITED, 7, Adam Street, Adelphi, in the County of London.
Printed by HAZELL, WATSON & VINEY, LTD., London and Aylesbury—Saturday, September 28, 1957.
PRINTED IN GREAT BRITAIN—Entered as Second Class at the New York, U.S.A., Office.

relief of cough

BENYLIN EXPECTORANT* is a rational and effective preparation containing Benadryl* and expectorants for the relief of cough associated with irritative and congestive conditions of the respiratory tract. It inhibits the cough reflex, alleviates congestive symptoms, such as nasal stuffiness, and exerts a soothing effect on the upper respiratory mucosa. Benylin Expectorant is presented as a pleasant raspberry-flavoured syrup, and as it is free from opiates is suitable for children as well as adults.

Trade Mark

Benylin Expectorant

demulcent · decongestant

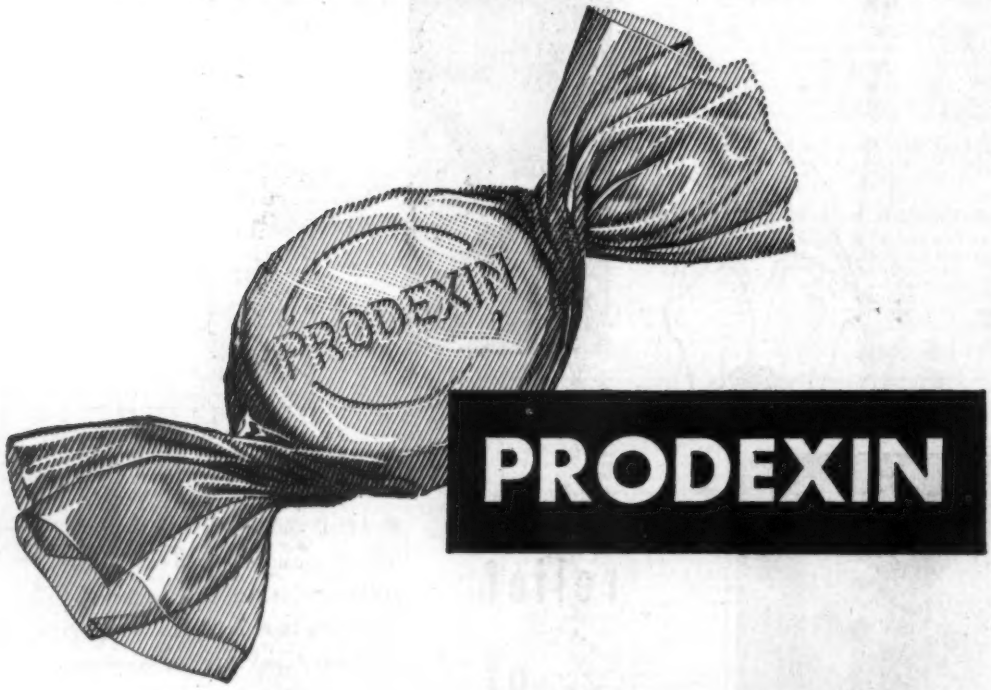
Supplied in bottles of 4, 16 and 80 fl. ozs.

Parke, Davis & Company, Ltd. *(Inc. U.S.A.)* Hounslow, Middx. Tel: Hounslow 2361

234

iii

PREDICTABLE *ANTACID THERAPY*



1 **rapidly relieves gastric pain**
2 **safely buffers excess acid**
3 **non-alkalising**
4 **non-constipating**
5 **stable, consistent and predictable**

Prodexin tablets sucked at regular intervals provide continuous buffering of gastric acid at about *p*H 4, no matter how acid the stomach contents or how often the stomach empties. Prodexin does not alkalise the stomach and does not stimulate compensatory secretion of acid. The tablets are pleasant to take, non-gritty and non-constipating.

PRODEXIN
Each Prodexin tablet contains:
Aluminium glycinate (dihydroxy aluminium aminoacetate).....0·9 gramme
Light magnesium carbonate.....0·1 gramme

Cartons of 30 singly wrapped tablets.

Dispensing packs of 240 tablets (basic N.H.S. cost 30/4d.)

601/60/2

C. L. BENCARD LTD. · PARK ROYAL · LONDON · N.W.10